Innovations in mental health care for adult depression

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Innovations in mental health care for adult depression

Results of a series of meta-analyses

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Colophon

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Innovations in mental health care for adult depression:
Results of a series of meta-analyses

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CONTENTS

Love, work, and knowledge are the wellsprings of our lives, they should also govern it.

Wilhelm Reich

PART I

General Introduction

CHAPTER 1

GENERAL INTRODUCTION

INTRODUCTION

This thesis aimed at providing recommendations for improving the mental health care of adult depression by reviewing existing research evidence. It consists of a series of conventional and individual patient data systematic reviews and meta-analyses that were conducted in an effort to expand the current knowledge on the short and long-term outcomes of psychotherapy, its costs, adherence and negative effects. More specifically, this thesis focused on long-term effects of psychotherapy alone or in combination with antidepressants, the effects of psychotherapy in low- and middle-income countries and on economic evidence for the clinical management of major depression. Further, a special attention was placed on Internet-based interventions as these interventions have the potential to overcome many treatment barriers and increase psychotherapy accessibility and availability.

SYSTEMATIC REVIEWS AND META-ANALYSES

What is a systematic review?

Systematic reviews are widely considered as the "gold standard" in evidence synthesis. A systematic review employs explicit methods to minimize bias and provide reliable findings and conclusions (Higgins & Green, 2008). It uses pre-specified objectives and eligibility criteria, reproducible methodology, systematic search of studies, assessment of studies validity and systematic synthesis and presentation of the findings (Higgins & Green, 2008). In a systematic review the results of the individual studies can be summarized either narratively or statistically. The statistical summary of the results of a systematic review is called meta-analysis.

Types of meta-analyses

There are several types of meta-analyses, including: a) traditional pairwise meta-analysis, b) network meta-analysis and c) individual participant data (IPD) meta-analysis. The conventional pairwise meta-analysis synthesises aggregate data from different trials evaluating the same intervention to calculate an overall treatment effect relative to a direct comparison (intervention vs. control) (Cuijpers, 2016; Jansen & Naci, 2013). However, in some cases all available trials of interest do not examine the same comparison but each of the trials examines a subset of this comparison. Thus, the conventional pairwise meta-analysis cannot be employed as it synthesises outcomes of direct comparisons. In these cases network meta-analysis is used, which is an extension of the conventional pairwise meta-analysis. A network-meta-analysis synthesises data from direct comparisons of interventions within RCTs and indirect comparisons across RCTs based on a common comparator (e.g. placebo) (Cuijpers, 2016; Jansen & Naci, 2013). Finally, many important research questions cannot be answered using aggregate data from study publications. For instance, questions such as "which patients' characteristics predict treatment dropout" require a different methodological approach. The meta-analysis of IPD is an increasingly popular approach to address questions related to predictors and moderators of treatment outcome. The IPD meta-analysis synthesises all raw individual data obtained from the trials of interest (Riley, Lambert, & Abo-Zaid, 2010).

Why systematic reviews are important?

Major stakeholders (e.g., policy makers, health care providers and patients) use systematic reviews to make decisions about treatments, develop treatment guidelines, and decide about which treatments should be included in the health care systems (Higgins & Green, 2008). In addition, researchers use the findings of systematic reviews to identify knowledge gaps and inform the development of future trials. Systematic reviews thus, are fundamental to evidence-based decision-making for several reasons. The rapid developments in psychotherapy research have led to a great number of RCTs examining the effectiveness of psychotherapeutic interventions. Results differ across these RCTs and are often conflicting. This large volume of evidence makes it impossible to draw one reliable conclusion about the effectiveness of a specific intervention (Cuijpers, 2016). Systematic reviews can reliably summarize the existing results and produce an overall effect estimate. In contrast with primary research, systematic reviews use a wide range of evidence from different countries and time periods. In this way, systematic reviews lead to a better understanding of the true effect of an intervention across different geographical regions and timescales. Moreover, systematic reviews employ explicit methodology to examine inconsistencies between the primary trials and differences between sub-groups of studies (Cuijpers, 2016). Finally, primary trials often lack the statistical power to examine important research questions, such as "which patients characteristics moderate treatment outcome". Novel methodological approaches, such as IPD meta-analysis, maximise the power to detect moderators of treatment outcome by synthesising all IPD data from primary trials on the topic of interest (Riley et al., 2010).

DEPRESSION

Depression is a mental disorder that affects daily functioning and it is characterised by low mood and diminished interest in most activities. Individuals with depression experience multiple persistent behavioural, physical, cognitive and psychosocial symptoms. Among depressive symptoms are significant changes in appetite, changes in sleep and activity, loss of energy, concentration problems, feelings of worthlessness and suicidal ideation (American Psychiatric Association, 2013). Depression is considered a major public health challenge worldwide due to its high prevalence, chronicity and disability (Üstün, Ayuso-Mateos, Chatterji, Mathers, & Murray, 2004b). Several epidemiological studies have shown that depression is amongst the most common of mental health disorders with a lifetime prevalence ranging from 3% in Japan to 17% in the United States (Andrade et al., 2003). Moreover, the World Health Organisation (WHO) estimates that more than 300 million individuals suffer from depression globally (World Health Organization, 2001).

Depression is not only highly prevalent but also disabling and often runs a chronic course. It has been estimated that approximately 60% of the individuals who had a major depressive episode once will experience a second one throughout their lifetime, while this percentage progressively increases to 70% and 90% for those who experienced two and three episodes respectively (Alladin, 2007). Furthermore, depression is associated with functional impairment

and it imposes an enormous burden on individuals and the society. More specifically, in 2015 the Institute for Health Metrics and Evaluation (IHME) reported that depression accounted for 2% of all disability adjusted life-years worldwide (IHME, 2015). Moreover, individuals with depression are at high risk of premature mortality mostly related to suicide as indicated by epidemiological evidence in both developed and developing countries (Nock et al., 2009). Results from the WHO world mental health surveys have shown that patients with depression are more likely to have several physical conditions, e.g. back/ neck problems (Scott et al., 2007) and poor outcomes on home management, work, social life and the ability to form and maintain close relationships (Ormel et al., 2008).

A large body of literature has shown that depression results in substantial societal burden related to productivity losses and healthcare utilisation with indirect costs outweighing the direct health care costs (Donohue & Pincus, 2007; Wittchen et al., 2011). Direct treatment cost arises from primary and secondary health care resources spent on both outpatient and inpatient treatment for depression (Philip S Wang, Simon, & Kessler, 2003). Moreover, previous literature has documented that depression leads to diminished labour participation and productivity since individuals with depression have fewer employment rates and report more absenteeism and presenteeism rates compared to those without depression (Alonso et al., 2011; Bruffaerts et al., 2012).

CURRENT FIRST-LINE TREATMENT APPROACHES FOR ADULT DEPRESSION

The aforementioned observations underline the necessity to provide effective treatment to individuals with depression. The treatment of adult depression is characterised by three phases: acute, continuation and maintenance. Acute phase treatment refers to an intervention occurring after the onset of depression and it is aimed at alleviating symptoms of an active depressive episode. In some cases, acute treatment is followed by continuation treatment, which is targeted at preventing relapse into the same episode of depression for which acute phase treatment was initiated. Finally, maintenance therapy is a prolonged treatment, which begins when the aim is to prevent future recurrence of depression (Gotlib & Hammen, 2008).

Pharmacotherapy

Currently pharmacotherapy is the frontline treatment for adult depression. The most commonly prescribed classes of antidepressant medications are selective serotonin reuptake inhibitors (SSRIs; e.g. fluoxetine) and serotonin-norepinephrine reuptake inhibitors (SNRIs; e.g. duloxetine). Other rarely used classes of antidepressants are tricyclic antidepressants (TCAs; e.g. amitriptyline), and monoamine oxidase inhibitors (MAOIs; e.g. tranylcypromine) (Qaseem, Barry, & Kansagara, 2016). In addition to antidepressants, doctors often prescribe other types of medications, such as mood stabilizers, antipsychotics and anti-anxiety pills. Antidepressants relieve depressive symptoms by targeting neurotransmitters that are considered to be associated with mood (Gotlib & Hammen, 2008).

A large body of literature has examined the absolute and relative effectiveness of antidepressants in treating depression. In 2011, Gartlehner et al. reported that "*current evidence does not warrant recommending a particular second-generation antidepressant on the basis of differences in efficacy*" as the authors found that there are no differences in the efficacy or effectiveness between different types of antidepressants in acute, continuation and maintenance treatment (Gartlehner et al., 2011). In 2008, Kirsch and colleagues obtained data that pharmaceutical companies had to send to the Food and Drug Administration (FDA) from all clinical trials that they had sponsored. In these data, 57% of the trials were negative or failed (Kirsch & Low, 2013). In further analyses the authors found a small effect in favour of antidepressants compared to pill placebo after acute phase treatment (d = 0.32), which increased for patients with severe depression and exceeded the criterion for clinical significance that was at that moment recommended in a NICE guideline (d = 0.50) (Kirsch et al., 2008; National Institute for Clinical Excellence, 2004). This small but significant effect in favour of antidepressants was also found by Turner and colleagues (2008) after accounting for selective publication of antidepressant trials (g = 0.31; 05% CU 0.27 – 0.35) (Turner, Matthews, Linardatos, Tell, & Rosenthal, 2008).

Previous research has extensively examined possible side effects of antidepressants. Different classes of antidepressants present different side effects, while side effects also vary within each class of antidepressants. First-generation antidepressants (TCAs and MAOIs) have a great range of side effects and, therefore, are rarely used in clinical practice nowadays (Qaseem et al., 2016). The MAOIs are associated with cardiovascular side effects, such as hypertensive crisis. Moreover, the TCAs present anticholinergic side effects (e.g. visual changes), while massive TCAs' overdose can cause severe toxicity. Second-generation antidepressants (e.g. SSRIs) are associated with less side effects compared to the oldest antidepressants (Gelenberg et al., 2010). However, for example the SSRIs may cause neurologic and sexual side effects, such as headaches or erectile dysfunction (Gelenberg et al., 2010; National Collaborating Centre for Mental Health, 2010b). Finally, antidepressant medications can cause discontinuation symptoms, such as irritability. However, it should be noted that there is no evidence indicating that antidepressants can cause psychological or physical dependence (National Collaborating Centre for Mental Health, 2010b).

Psychotherapy

Recent treatment guidelines suggest the use of psychotherapeutic interventions as a first-line treatment for individuals with mild to moderate depression (Gelenberg et al., 2010; National Collaborating Centre for Mental Health, 2010b; Parikh et al., 2009). Psychotherapy is more resource intensive compared to pharmacotherapy in terms of costs of labour. Therefore, it is currently offered to a lesser degree in primary care, although many patients with depression prefer psychotherapy to antidepressants (McHugh, Whitton, Peckham, Welge, & Otto, 2013; van Schaik et al., 2004). Main types of psychotherapeutic interventions are: Cognitive Behaviour Therapy (CBT), Behavioural Activation (BA), Psychodynamic Psychotherapy (PDT), Problem Solving Therapy (PST), Interpersonal Psychotherapy (IPT), Nondirective Supportive Therapy (SUP) and Social Skills Training (SST) (Cuijpers, van Straten, Andersson, & van Oppen, 2008a).

CBT is one of the best-established psychotherapeutic interventions for adult depression. According to cognitive theory, depression is maintained by maladaptive thoughts such as negative self-perception. These thoughts are organised into negative cognitive schemata, which dominate information processing and consequently affect the behaviour and feelings of individuals with depression. CBT teaches individuals the way to recognise these maladaptive thoughts and modify them into adaptive thoughts, thereby leading to behavioural changes (Dobson & Dobson, 2016; Gotlib & Hammen, 2008). BA is a behavioural therapy, which emerged from component analyses of CBT (Jacobson et al., 1996). According to behaviour theory, depression results from reduced environmental reward and positive reinforcement due to environmental changes and avoidant behavioural patterns (Carvalho & Hopko, 2011; Lewinsohn, 1974). Core elements of BA treatment are the enchantment of both positive activities and positive environmental interactions (Cuijpers, van Straten, et al., 2008a). PST is also a cognitive behavioural intervention, which aims at improving the ability of individuals with depression to cope with stressful life events (e.g. losing a job) (D'Zurilla & Nezu, 1999). Patients following PST learn how to develop a plan of multiple solutions for a specific problem as well as how to execute and evaluate this plan (Cuijpers, van Straten, et al., 2008a).

PDT is based on psychoanalytic theory, the basic principle of which is that psychosexual developmental stages should be completed successfully to develop a healthy personality. Early childhood experiences play an important role in the development of personality and influence behaviour later in life (Etchegoyen, 2005). PDT focuses on enhancing patient's awareness about intrapsychic and intrapersonal unresolved conflicts from the past, which influence patient's function in the present (Cuijpers, van Straten, et al., 2008a). IPT is a time-limited psychotherapeutic treatment based on interpersonal theory. The general principle is that interpersonal relationships and life events affect depressed mood and vice versa (Gotlib & Hammen, 2008; Markowitz, Svartberg, & Swartz, 1998). IPT basic strategy is to reduce symptoms of depression by resolving interpersonal problems and consequently improving patients' life situation (Gotlib & Hammen, 2008). Other types of psychotherapy, such as SUP and SST focus on relieving depression through discussion with others and through training patients in assertiveness respectively (Cuijpers, van Straten, et al., 2008a). An overview of the effects of psychotherapy is given in the following sections.

EFFECTS OF PSYCHOTHERAPY ON ADULT DEPRESSION

During the past decades a growing body of literature has addressed the absolute and relative efficacy of psychotherapeutic interventions for adult depression. These studies have clearly illustrated that acute, continuation and maintenance psychotherapy is effective in treating adult depression.

Psychotherapy versus controls

In 2011, Cuijpers et al. examined the results of 147 studies comparing psychotherapy to control conditions (waiting list, treatment as usual and other non-active controls) and showed

that psychotherapy was superior to controls after excluding outliers (d = 0.53). However, this effect was smaller for studies comparing psychotherapy to treatment as usual and larger for those conducted in non-Western countries (Cuijpers, Andersson, Donker, & van Straten, 2011). The authors attributed these different effects to the fact that treatment as usual in Western countries includes in many case active treatments (e.g., antidepressants), while in non-Western countries usual care is mainly an inactive control condition (Cuijpers, Andersson, et al., 2011). In the same overview of a series of meta-analyses, Cuijpers et al. presented results showing that the superior effects of psychotherapy over controls are robust in specific target populations (Cuijpers, Andersson, et al., 2011). The authors presented ample evidence showing that psychotherapy is effective in treating older adults, women with postpartum depression, patients with comorbid physical disorders (e.g., diabetes), patients recruited from clinical samples (e.g., primary care patients) and patients with a specific diagnosis (e.g., Subthreshold depression) (Cuijpers, Andersson, et al., 2011). Furthermore, individual acute-phase psychotherapy seems more effective compared to group psychotherapy as it results in better outcomes compared to controls and higher adherence rates, although the quality of this body of research is not robust enough (Cuijpers, van Straten, & Warmerdam, 2008). Finally, a meta-analysis of 92 studies examining remission rates of psychotherapy for major depression found that 62% and 48% of patients did not meet criteria for major depression at the post-test in psychotherapy and controls respectively (Cuijpers et al., 2014).

With regards to the absolute efficacy of different types of psychotherapy, CBT, the most extensively examined psychotherapeutic treatment for depression, was found to be superior to non-active control conditions (g = 0.72) (Cristea et al., 2017). Moreover, BA treatments result in better depression outcomes compared to controls at post-treatment assessment (d = 0.87) (Cuijpers, van Straten, & Warmerdam, 2007a). In a meta-analysis of 13 randomised controlled trials (RCTs), PST presented an overall standardized effect of 0.83 compared to non-active controls, which varied considerably in several subgroup analyses (Cuijpers, van Straten, & Warmerdam, 2007b). IPT for acute phase depression resulted in a moderate effect size in a meta-analysis of 31 RCTs (d = 0.60), while type of recruitment and diagnosis were associated with the effects (Cuijpers, Donker, Weissman, Ravitz, & Cristea, 2016). Finally, brief PDT was found to be more effective than non-active controls in a meta-analysis of 23 studies conducted by Driessen et al. (d = 0.69) (Driessen, Cuijpers, de Maat, et al., 2010).

Although psychotherapy presents moderate to large effects, it should be noted that there are indications that these effects have been overestimated. In 2015, Driessen et al. collected data from unpublished funded psychotherapy trials and combined them with data from published trials. The authors found that adding unpublished studies (g = 0.20) to published (g = 0.52) results in a reduced but significant effect size of g = 0.39 in favour of psychotherapy compared to controls (Driessen, Hollon, Bockting, Cuijpers, & Turner, 2015). Furthermore, in another meta-analysis examining the influence of study quality on psychotherapy outcomes, the authors found that high-quality studies had smaller effects (d = 0.22) than lower quality studies (d = 0.75) (Cuijpers, van Straten, Bohlmeijer, Hollon, & Andersson, 2010b).

Relative efficacy of different psychotherapeutic types

There is a long-standing debate in psychotherapy research over the "dodo bird verdict", which named after the Dodo bird fictional character's phrase *"Everybody has won, and all must have prizes"* from the tale "Alice's Adventures in Wonderland". Supporters of the "dodo bird verdict" claim that if different psychotherapeutic types are equally effective, it is because psychotherapeutic interventions share common factors, such as therapeutic alliance (Luborsky, 1995). Opponents of this theory support that specific factors must account for treatments outcomes since different psychotherapeutic types produce different outcomes for particular disorders (Siev & Chambless, 2007; Siev, Huppert, & Chambless, 2009). For instance, Turner and colleagues showed that psychotherapies differ in the effects on psychosis, thereby rejecting the "dodo bird verdict" (Turner, van der Gaag, Karyotaki, & Cuijpers, 2014)

In the case of depression, results from several meta-analyses have shown that main psychotherapeutic types are equally effective when compared directly to each other. In a meta-analysis of 53 trials, there was no indication that the effects of main psychotherapeutic treatments for depression differed with an exception of IPT and SUP, which was slightly more and less efficacious respectively (Cuijpers, Annemieke van Straten, et al., 2008a). Thus, so far research outcomes on psychotherapies for depression seem to support the "dodo bird verdict" as there is no evidence showing the contribution of specific treatment factors (e.g. cognitive restructuring in CBT) to psychotherapies effects. However, drawing conclusions based on the existing evidence is premature since there are still many questions that need to be answered regarding the relative efficacy of different psychotherapies and treatment factors. For example, little is known about the long-term efficacy of different psychotherapies in treating adult depression (Cuijpers, 1998).

Psychotherapy versus Pharmacotherapy

Several trials have compared the effects of psychotherapy to pharmacotherapy in treating depression. Results from a meta-analysis of direct comparisons showed that there was no significant difference between the effects of psychotherapy and antidepressants on major depression at the post-treatment assessment, while antidepressants presented slightly higher effects on Dysthymia (Cuijpers, Sijbrandij, et al., 2013). At the long term, CBT outperformed antidepressants when only patients who discontinued medication during follow-up were included in the analysis. However, there was no significant difference between the effects of CBT and antidepressants continuation over the long term (Cuijpers, Steven Hollon, et al., 2013). Previous treatment guidelines have suggested that antidepressants should be preferred over psychotherapy for severe depression (Anderson et al., 2008; Gelenberg et al., 2010). However, a recent large meta-analysis of individual patient data (IPD) showed that baseline severity did not influence the post-treatment outcomes between psychotherapy and antidepressants (Weitz et al., 2015). The authors did find a small significant effect in favor of antidepressants over CBT on the Hamilton Rating Scale for depression (HAM-D), which was not replicated when the outcomes on BDI were examined (Weitz et al., 2015). Overall, psychotherapy and

antidepressants seem to have very small to non-existent differences that are not influenced by initial symptom severity.

Combined Psychotherapy with pharmacotherapy

For severe depression, current treatment guidelines recommend the combination of psychotherapy with pharmacotherapy and suggest that monotherapy (either psychotherapy or pharmacotherapy alone) should be preferred for mild to moderate depression (Koran, Hanna, Hollander, Nestadt, & Simpson, 2007). Previous literature has shown that combined treatment is more effective than monotherapy in the short-term (Cuijpers, 2014). Results of a meta-analysis of 53 RCTs indicated that combined treatment results in a superior moderate effect against pill placebo (g = 0.46) and small to moderate effects compared to antidepressants (g = 0.38), psychotherapy (g = 0.34) and the combination of psychotherapy and pill placebo (0.31) at post-treatment assessment (Cuijpers, de Wit, Weitz, Andersson, & Huibers, 2015).

BARRIERS TO PSYCHOTHERAPY

As has been demonstrated above, psychotherapy is effective in treating depression. However, a substantial number of individuals with depression do not receive any treatment (Wang et al., 2005). Moreover, many of those who receive treatment drop out before treatment completion (Mojtabai et al., 2011; Wang et al., 2007). Poor rates of help seeking and service use undermine the effort of providing effective treatment for depression. Data from a large-scale epidemiological survey in Europe have shown that only 14% of individuals with mood disorders received psychological treatment, while 38% received pharmacotherapy (Alonso et al., 2004a). This percentage is even lower in low- and middle-income countries where only 7-21% of the population receive treatment (Chisholm et al., 2016). Recently, there has been growing interest in understanding barriers to the uptake of evidence-based interventions.

The most common barriers to psychotherapy are structural, e.g. cost related to the provision of mental health care, time constraints of patients and in some countries transportation barriers (Mohr et al., 2010). The cost of care is one of the most important obstacles of depression treatment provision. According to economic analyses of health care utilisation, the use of treatment services is inversely proportional to the price of these services (Bunney, Kleinman, Pellmar, & Goldsmith, 2002). In other words, the higher the price, the lower the use and the provision of therapy, while the use increases when the treatment expenses are reimbursed, by, for instance, insurance companies (Bunney et al., 2002). Other structural barriers to psychotherapy are health care budget shortages, the availability of health care services and the limited number of trained clinicians (World Health Organization, 2010). Even well endowed mental health care systems may find it difficult to marshal enough qualified therapists to offer interventions. This is particularly evident in low and middle-income countries where mental health care facilities are scarce (World Health Organization, 2010).

Research evidence has shown that stigma fears related to diagnosis and treatment of depression play an important role in underutilization of mental health care services. Stigma is defined as *"the co-occurrence of labelling, stereotyping, separation, status loss and discrimination"* and has severe implications in health and quality of life (Link & Phelan, 2001). Mental health stigma has several sub-types, for instance it can be internalised, perceived or related to treatment. Individuals with depression may internalize mental illness stigma and experience low self-esteem (internalised stigma) (Clement et al., 2015). However, stigma may also be related to external factors, e.g. individual's views regarding believes about mental illness that other people might hold (perceived stigma) or stigma related to seeking or receiving mental health treatment for depression (treatment stigma) (Clement et al., 2015). Both internalized and treatment stigma negatively influence treatment seeking rates (Clement et al., 2015).

Other obstacles are patients' attitudes towards depression and treatment (Mojtabai et al., 2011). Low perceived need for treatment is a commonly reported barrier to treatment seeking. Many individuals with depression believe that they do not need to seek help for their symptoms (Sareen et al., 2007). Among those who do recognise the importance of treatment, the desire of managing depression on their own is the most commonly reported reason for not seeking treatment (Mojtabai et al., 2011). Moreover, many individuals with depression are pessimistic regarding the effectiveness of the available treatments (Mojtabai et al., 2011). However, it should be noted that reasons for not seeking treatment vary across depression severity with more severely depressed adults reporting less frequently attitudinal reasons and more frequently accessibility issues related to financial barriers (Mojtabai et al., 2011; Wang et al., 2007).

Internet based Self-help for depression

During the last decades, the rapid development and use of information technology led to innovative treatment approaches, such as Internet-based interventions. Internet-based psychotherapy is a form of psychotherapy in which a patient follows structured sessions via Internet. These interventions can be either guided or unguided. Guided Internet-based interventions include minimal or more extensive therapeutic support that can be delivered by a clinician or a trained coach (Cuijpers, Kleiboer, Karyotaki, & Riper, 2017; Titov et al., 2010). Unguided Internet-based interventions may involve automated feedback but do not provide any professional support related to the therapeutic content. However, in some cases unguided interventions are delivered with support related to technical problems that patients may experience when they use the intervention. Internet-based interventions offer a number of potential advantages which may overcome a number of the face to face psychotherapy barriers that include reducing treatment cost, overcoming stigma fears, and increasing accessibility and availability of evidence-based treatment (Andersson, Cuijpers, Carlbring, Riper, & Hedman, 2014a; Donker et al., 2015). Moreover, Internet-based psychotherapy reduces clinicians' time and allows patients to follow the treatment at their own pace (Cuijpers, van Straten, & Andersson, 2008; Titov, 2011).

A growing body of literature has addressed the effectiveness of Internet-based and other computerized psychotherapeutic programmes for adult depression. Since 2002, a rapidly increasing number of RCTs have compared the effects of several types of Internet-based psychotherapy (e.g., iCBT, iPST and iPDT) to control conditions (e.g., waiting list, attention placebo or treatment as usual) (Andersson et al., 2005; Berger, Hammerli, Gubser, Andersson, & Caspar, 2011; Clarke et al., 2002; Farrer, Christensen, Griffiths, & Mackinnon, 2011; Kleiboer et al., 2015; Spek, Cuijpers, et al., 2007; Titov et al., 2015). Results so far show that guided Internet interventions produce significantly higher effect sizes compared to control conditions (Andersson & Cuijpers, 2009; Richards & Richardson, 2012; Spek, Cuijpers, et al., 2007) and have comparable outcomes with conventional face-to-face treatments (Andersson et al., 2014a). Moreover, compliance rates of guided iCBT or more generic internet-based IPT are relatively high and comparable with face-to-face psychotherapy (van Ballegooijen et al., 2014).

Unguided interventions have low cost and can be easily disseminated to large numbers of people with depression, thereby increasing even further treatment availability. However, research evidence for unguided Internet-based psychotherapy presents variation. Trials comparing self-guided interventions to control conditions have shown results ranging from no difference (Gilbody et al., 2015; Phillips et al., 2014) to a substantial beneficial effect (Klein et al., 2016; Meyer et al., 2015). In addition, dropout rates in unguided interventions are high with only about 30% of participants completing treatment (Richards & Richardson, 2012). Thus, unguided Internet-based treatment appears to be less promising compared to guided interventions. However, conclusions regarding the relative efficacy of guided and unguided interventions should be drawn cautiously since current evidence derives mostly from indirect comparisons. Studies of direct comparisons have shown no differences between the effectiveness of guided and unguided Internet-based interventions (Berger, Hammerli, et al., 2011).

GAPS IN CURRENT KNOWLEDGE

Although much has been achieved in psychotherapy research over the past decades, we still have not answered essential questions regarding the effectiveness of psychotherapy.

Long-term effects of psychotherapy and Combined treatment

As discussed above, psychotherapy outperforms control groups in treating adult depression in the short-term (Cuijpers, Andersson, et al., 2011). Moreover, psychotherapy and pharmacotherapy have similar effects (Cuijpers, Sijbrandij, et al., 2013), while combined treatment (psychotherapy with pharmacotherapy) seems superior to monotherapy at the post-treatment assessment (Cuijpers, 2014). However, it remains unclear whether the effects of psychotherapy or combined treatment last beyond the end of treatment sessions. It has long been claimed that in psychotherapy patients learn skills that they can use after the end of acute treatment to prevent future relapse. In contrast, similar claims have not been made about the long-term effects of pharmacotherapy (Cuijpers, Hollon, et al., 2013). It should be noted that antidepressant continuation is the norm rather than the exception and in some cases

(e.g. chronic depression) patients receive pharmacotherapy indefinitely. As mentioned above, meta-analytic evidence has shown that CBT results in better long-term effects on depression compared to antidepressant discontinuation, while these favourable CBT effects disappear when compared to antidepressants continuation (Cuijpers, Hollon, et al., 2013). Nevertheless, it remains unclear whether acute psychotherapy results in better enduring effects compared to control conditions. Moreover, it is unclear how combined treatment compares with either psychotherapy or pharmacotherapy alone over the long-term. From a clinical perspective, it is important to expand our knowledge on the long-term outcomes of psychotherapy and combined treatment. Such knowledge will support clinicians and patients in making informed decisions related to therapeutic modality.

Effects of psychotherapy in low and middle income countries

The vast majority of the world population live in low- and middle-income countries (Jacob et al., 2007). Sadly, as mentioned above, a great percentage of those who live in these countries and experience depression do not receive treatment mostly due to scarcity of mental health resources (Chisholm et al., 2016; World Health Organization, 2010). It should be noted that pharmacotherapy is the most commonly prescribed treatment in low- and middle-income countries, while psychotherapy is offered to a lesser degree. Although the effectiveness of psychotherapy in treating depression is well established, most of the evidence derives from high-income countries (Weinmann & Koesters, 2016). It remains thus, unclear whether psychotherapeutic interventions primarily designed for high-income countries are also effective in low- and middle-income counties. Further examination of the effectiveness of psychotherapy in low- and middle-income countries will give important insights into the use of psychotherapeutic interventions in different regions.

Cost effectiveness of psychotherapy

As reported above, numerous RCTs and systematic reviews have demonstrated that psychotherapy is effective in treating adult depression (Cuijpers, Andersson, et al., 2011). However, patients with depression are mostly treated with antidepressants because psychotherapy is considered more resource intensive. Healthcare systems face many challenges in providing effective treatments and maintaining budgetary stability. Given the rising cost of mental health care over the past decade, cost-effectiveness research is needed to ensure treatment accessibility and feasibility. However, it remains unclear whether the existing treatments for depression are cost-effective. Further research is needed to examine the existing economic evidence on treatments for depression. Such research will contribute to clinical decision-making by shedding light on the cost-effectiveness of psychotherapy.

Internet-based psychotherapy: adherence, effectiveness and deterioration rates.

Internet-based psychotherapeutic interventions may overcome many of psychotherapy barriers (Andersson et al., 2014a; Donker et al., 2015). Although the effects of guided-interventions are comparable to those of face-to-face treatment (Andersson et al., 2014a), the effects of purely

self-guided interventions appear inconclusive (Gilbody et al., 2015; Phillips et al., 2014) to a substantial beneficial effect (Klein et al., 2016; Meyer et al., 2015).

As maintained above, unguided interventions have the potential to further increase treatment accessibility and reduce treatment costs. However, as mentioned above, trials of unguided interventions have shown mixed outcomes, suggesting that the effectiveness of such interventions is uncertain (Gilbody et al., 2015; Meyer et al., 2015; Phillips et al., 2014). Moreover, there is a gap in understanding who benefits from unguided Internet-based psychotherapy. For instance, we still do not know whether the effects of unguided Internet-based psychotherapy are influenced by baseline depression severity. Furthermore, previous reviews have suggested that low adherence rates might negatively influence treatment outcomes. This is of particular importance for self-guided interventions that present very low adherence rates (Donkin et al., 2011). If adherence influences treatment outcomes, it is important to further examine predictors of treatment adherence in self-guided Internet-based interventions. Such examination will provide valuable knowledge regarding who is at risk for dropping out before treatment completion. Finally, it has been claimed that the lack of therapeutic support may pose a risk to treatment outcomes (Newman, Erickson, Przeworski, & Dzus, 2003). Nevertheless, undesirable treatment outcomes, such as deterioration rates, have been rarely reported in psychotherapy research in general and specifically for iCBT. Thus, it is important to further examine whether unguided Internet-based treatment is a safe treatment option for adult depression.

Research evidence has shown that guided interventions are effective in reducing depressive symptoms and present high adherence rates (Richards & Richardson, 2012). However, several questions regarding the effects of guided interventions remain unanswered. More specifically, little is known about the effects of guided interventions on important clinical outcomes, such as remission and treatment response. Moreover, like the unguided interventions, we still do not know for whom Internet-based guided psychotherapy works. For example, it is still not clear whether guided interventions result in equal chance for remission in both genders, or whether patients with comorbid anxiety respond to guided interventions equally with those without. Further research on this field will provide valuable insights into the development of guided interventions.

THESIS OUTLINE

To give answers to the questions raised above, all existing empirical evidence should be collated and systematically summarized. Thus, the present thesis employs the methodology of systematic reviews and meta-analysis to solve existing knowledge gaps. The thesis consists of two main parts. The first part presents the results of a series of systematic reviews and traditional pairwise meta-analyses synthesising aggregate data from published RCTs. **Chapter 2** presents the long-term effects of acute phase psychotherapy on depression and quality of life compared to no treatment control conditions. **Chapter 3** shows the long-term effects of

acute and maintenance combined treatment (psychotherapy with pharmacotherapy) in treating major depression compared to monotherapy (either psychotherapy or pharmacotherapy alone). **Chapter 4** examines the effects of psychotherapy in low- and middle-income countries and **Chapter 5** is a narrative systematic review showing an overview of the economic evidence for the clinical management of major depression.

The second part of this thesis comprises five chapters that examine in depth the effects of Internet-based interventions in treating adult depression by means of IPD meta-analyses. **Chapter 6** presents the effects of self-guided Internet-based CBT in reducing depressive symptoms and in treatment response compared to control groups. Moreover, it examines several individual- and study level moderators of treatment outcome. **Chapter 7** gives a response to concerns raised regarding the interpretation of the finding of chapter 6. **Chapter 8** examines predictors of treatment dropout in self-guided Internet-based psychotherapy for depression. **Chapter 9** focuses on deterioration rates of self-guided Internet-based CBT compared to control groups. In addition, it evaluates the moderating effects of several individual- and study level variables on treatment outcome. **Chapter 10** describes the effects of guided Internet-based psychotherapy on depression remission and response as compared to control groups. This chapter also examines the moderating effects of several individual- and study-level variables.

Finally, the present thesis is concluded with **Chapter 11** that is a general discussion of the present findings, which includes limitations, suggestions for future research and implications for clinical and research practice.

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PART II

Conventional Systematic Reviews & Meta-Analyses

CHAPTER 2

THE LONG-TERM EFFICACY OF ACUTE PHASE PSYCHOTHERAPY FOR DEPRESSION: A META-ANALYSIS OF RANDOMIZED TRIALS

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ABSTRACT

Background:
Understanding the effectiveness of treatment for depression in both the short-term and long-term is essential for clinical decision-making. The present meta-analysis examined treatment effects on depression and quality of life in acute phase psychotherapeutic interventions compared to no treatment control groups for adult depression at six months or longer post-randomization.

Methods:
A systematic literature search resulted in forty-four randomized controlled trials with 6096 participants. Acute phase psychotherapy was compared to control groups at 6 month or longer post-randomization. Odds ratios of a positive outcome were calculated.

Results:
Psychotherapy outperformed control groups at six months or longer post-randomization (OR = 1.92, 95% CI: 1.60 to 2.31, $p < 0.001$). Heterogeneity was moderate (I^2: 65, 95% CI: 53 to 74, $p < 0.001$). However, effects significantly decreased with longer follow-up periods. Additionally, a small positive effect of psychotherapy was observed for quality of life, while similar effects were obtained in separate analyses of each type of psychotherapy, with the exception of non-directive supportive therapy. Studies that provided booster sessions had better treatment results compared with studies that did not provide any further sessions. Finally, we found that trials on psychotherapy aimed at Major Depressive Disorder (MDD) had better outcomes than those that were aimed at elevated depressive symptoms.

Conclusions:
There is substantial evidence that acute phase psychotherapy results in a better treatment effects on depression and quality of life in the long-term for adult patients with depression.

INTRODUCTION

Depression, a highly prevalent and disabling disorder, constitutes a major public health issue worldwide. Epidemiological studies have shown that 14.6 per cent of individuals in developed countries have experienced a major depressive episode at some point throughout lifetime (Bromet et al., 2011). In addition to high prevalence rates, depression is currently ranked first among mental disorders with regards to disease burden, according to the World Health Organization (Reddy, 2010). This disease burden results from the large impact of depressive disorder on individuals' lives, as depression adversely affects quality of life. Depressive disorder is also associated with increased mortality rates and high economic and societal cost (Andrews, Henderson, & Hall, 2001; Rapaport, Clary, Fayyad, & Endicott, 2005). Additionally, depression has high relapse rates, which in turn increase the chance of depression developing into a chronic condition (Kessler et al., 2005; Kruijshaar et al., 2005). Keller (1994) estimated that individuals who have experienced one episode of depression have 50 per cent chance of experiencing a second episode, while those who have experienced a second episode have 90 per cent chance of experiencing a third (Keller, 1994).

The high adverse impact of depression on individuals' lives underscores the need for treatment. Maintenance pharmacotherapy is currently the most widely used treatment in preventing relapse of depressive episodes. Antidepressant medication reduces the risk of relapse, especially when used for long periods of time (Geddes et al., 2003). However, a notable number of patients have a preference for short-term use of antidepressants resulting in low adherence to medication and leading to recidivism. Moreover, research has shown that a considerable percentage of individuals with depression prefer psychotherapy to pharmacotherapy (van Schaik et al., 2004). Psychotherapy aims at helping individuals to develop adaptive mechanisms in order to be more functional in their lives and to effectively cope with depression. Psychotherapy intends to alleviate symptoms of an active depression but also works to prevent future relapses and maintain the favourable treatment response over a lengthy period of time.

It is well known that acute phase psychotherapy (psychotherapy targeted at an active depression) is effective in the treatment of depressive disorders in short-term. For instance, a recent meta-analysis carried out by Cuijpers et al. (2013) examined the effects of Cognitive Behavioural Therapy (CBT) in treating adult depression. The authors found a large effect size in favour of CBT compared to control groups (d = 0.71) at the post-treatment assessment (Cuijpers, Berking, et al., 2013b). Similar results have been presented for several other major types of psychotherapy, such as interpersonal psychotherapy (Cuijpers, Geraedts, et al., 2011) and behavioural activation (Ekers et al., 2014). Despite these favourable short-term effects, there is little rigorous meta-analytic evidence regarding long-term outcomes of psychotherapy on depression.

Given the high risk of relapse, it is critical to examine whether psychotherapy results in an enduring effect on depression. Poor long-term outcomes lead to increased health care service

utilization and consequently to higher costs for the public healthcare system (Markowitz, 2008). Results derived from a meta-analysis by Piet et al. (2011) showed that maintenance mindfulness-based cognitive therapy (MBCT) resulted in a better reduction of depressive symptoms in comparison with treatment as usual or pill placebo at six months follow-up (Piet & Hougaard, 2011). This corresponds to a relative risk reduction of 34 per cent in favour of MBCT (Piet & Hougaard, 2011). These results are in accordance with the meta-analysis of Biesheuvel-Leliefeld et al. (2015). The authors examined the effectiveness of maintenance psychotherapy compared to treatment-as-usual (TAU) in reducing relapse or recurrence in patients with major depressive disorder (MDD). The results indicated that maintenance psychotherapeutic interventions reduced significantly the risk of relapse (RR = 0.64) in patients with MDD (Biesheuvel-Leliefeld et al., 2015).

To the best of our knowledge there is no systematic review that has examined the long-term effects of acute phase psychotherapy compared to control groups. Such a systematic review would extend our knowledge from short-term to long-term outcomes and would assist us in guiding clinical decisions and planning processes regarding depression treatment strategies in primary and secondary mental health care. Moreover, it would give an indication of the number of patients that maintain treatment response in the long-term, after receiving acute phase psychotherapy. The aim of the present meta-analysis is to examine long-term treatment effects on depression and quality of life at 6 months or longer post randomization to either acute phase psychotherapy for depression or a control group. The hypothesis is that psychotherapeutic interventions will outperform the control groups on depression and quality of life at six months or longer post-randomization.

METHODS

Definitions

Psychotherapy was defined as an intervention in which either verbal communication between a therapist and a client is the core element, or in which a psychological treatment is contained in book (bibliotherapy) or electronic format (internet-based treatment), which a patient works through more or less independently, but with some personal support from a therapist (guided by telephone, e-mail, or otherwise) (Cuijpers, Annemieke van Straten, et al., 2008a). In the present meta-analysis, we used a definition of psychotherapy based on taxonomy of psychotherapy types for depression developed by a group of experts in the field (Cuijpers, van Straten, et al., 2008a). The classification was based on a systematic search for studies on psychological treatments for depression, using broad definitions for psychotherapy. This process resulted in seven major types of psychotherapy for depression: behavioural activation (BA), cognitive behavioural therapy (CBT), interpersonal psychotherapy (IPT), non-directive supportive therapy (SUP), psychodynamic psychotherapy (DYN) and social skills training (SST) (see Appendix B3)

Acute phase psychotherapy was defined as the short-term psychotherapy delivered during the occurrence of depressive symptoms, as opposed to maintenance psychotherapy that can be delivered during remission/recovery of depressive symptoms.

Inclusion criteria

We selected randomized controlled trials (RCTs) including adult patients with depression (based on a clinical interview or on elevated depressive symptoms ratings on symptom scales). The selected interventions were all main psychotherapeutic interventions (as described above), while the selected comparison groups were usual care, waiting list, no treatment (no pharmacotherapy) or pill placebo. Light therapy or other types of psychotherapy, not defined as a main type of psychotherapy according to the definition described above, were not considered eligible as a comparison. We only included studies published and written in English

Search strategy

We searched Medline (PubMed.com), PsycINFO (Ebsco), Embase (embase.com) and the Cochrane library (cochranelibrary.com) from database inception to 1/1/2015. We used index and text words indicating psychotherapy combined with key terms for depression. We used a filter for RCTs as recommended in the Cochrane Handbook (Higgins & Green, 2011). The full search string for PubMed is given in Appendix A. Additionally; we searched an existing database on psychological treatments for depression in order to increase the probability of identifying eligible citations. This database has been developed and updated through literature searches in PubMed, PsycINFO, Embase and the Cochrane Central Register of Control trials from January 2006 until January 2015 (Cuijpers, van Straten, Warmerdam, & Andersson, 2008). Furthermore, references of selected studies were searched to identify additional relevant studies. Two reviewers (EK and YS or DB or EW) independently examined abstracts for eligibility. Studies that met inclusion criteria were examined in full text. In the case of disagreement, the opinion of a third reviewer (PC) was sought.

Data extraction

The following data were extracted: reference, years of inclusion, country, patient characteristics (e.g. target group: adults in general, specific target group, such as older adults, women with postpartum depression, etc.), therapy characteristics: type of psychotherapy, number of treatment sessions etc.), control characteristics: (e.g. type of control), and type and length of follow-up period. Most studies in this field used a naturalistic follow-up. Therefore, for each study we reported how long the follow-up period lasted, but also whether there was regular contact with a therapist. In some studies, outcome data were only reported for patients who responded to treatment in the acute phase treatment phase, while others reported outcomes for the full intention-to-treat sample. Two reviewers (EK and DB) extracted data independently; a third reviewer (PC) checked the data extraction.

Quality assessment

The quality of the included RCTs was examined by two reviewers (EK and YS or DB) independently, according to Cochrane Risk of Bias tool (Higgins & Altman, 2008). Any disagreement between the reviewers was solved through discussion.

Statistical analysis

We focused on all positive dichotomous outcomes on depression. In the context of the present paper, this combination of all positive outcomes is defined as 'all positive outcomes combined'. For the examined comparison between psychotherapy and control conditions we calculated the odds ratio (OR) of all positive outcomes combined based on dichotomous results. The following outcomes were extracted from the studies and were entered into the analysis hierarchically (when the first outcome in the hierarchy was not available the next available outcome was used):

i. Recovery (absence of depressive symptoms for ≥ 4 months after remission)
ii. Remission (No depressive symptoms; BDI I & II < 11; HAMD-17 & 21 < 8; MADRS < 7; PHQ-9 < 5)
iii. Partial Remission (No depressive symptoms or mild depressive symptoms; BDI I & II < 14; HAMD-17 & 21 < 14; MADRS < 20; PHQ-9 < 10)
iv. Response (50% reduction from baseline severity on any depression measure)
v. If no dichotomous outcomes were reported, we calculated the standardized mean difference (SMD) as the difference in mean scores divided by the pooled standard deviation. Subsequently, the mean difference was transformed into the OR according to the procedures given by Borenstein et al. (2009).

For dichotomous outcomes all randomized patients were taken as the denominator and reported outcomes in completers were taken as the numerator, thus simulating a last-observation-carried-forward-procedure. We also conducted meta-analyses for recovery, remission, partial remission and response rates separately.

Regarding the outcome quality of life, we calculated the effect sizes (Hedges's g) for the global quality of life (social functioning, physical and mental health). Hedge's g allows for small sample bias correction and is calculated by subtracting the average score (on global quality of life) of the psychotherapy group from the average score of the control group (at the follow-up) and dividing the results by the pooled standard deviation (Hedges L, 2001).

We calculated pooled odds ratios using the Comprehensive Meta-Analysis (version 2.2.021) programme. We expected considerable heterogeneity among the studies, so we used a random effects model to pool the results of the included RCTs.

The statistical heterogeneity was examined for all the outcomes of the present meta-analysis. This type of heterogeneity refers to the variability of the intervention effects between the included studies and indicates how much of the variability between studies can be explained by chance alone. Statistical heterogeneity can be caused by variability among the participants, interventions, outcomes and design of the included studies (Deeks, Higgins, & Altman, 2008). The I^2-statistic, an indicator of heterogeneity in percentages, was calculated in order to examine the homogeneity of the effect sizes. Heterogeneity was not observed if the resulted value of I^2 = 0%, as low when I^2 = 1% to 25%, as moderate when I^2 =26% to 74% and as high when $I^2 \geq 75\%$. We calculated 95% confidence intervals (CI) around I^2 (Evangelou, Ioannidis, & Patsopoulos, 2007) using the non-central chi-squared-based approach within the heterogi module for Stata (Orsini, Bottai, Higgins, & Buchan, 2006). The Q-statistic was calculated, and reported when significant.

We examined publication bias by examining the funnel plot on primary outcome measures and by using the Duval and Tweedie's trim and fill procedure (2000) (Duval & Tweedie, 2000). This procedure provides an estimate of the effect size after adjusting for publication bias (as implemented in Comprehensive Meta-analysis, version 2.2.021). Finally, we used Egger's test of the intercept to test the asymmetry of the funnel plot and examine whether this possibility of publication bias was significant (Egger, Smith, Schneider, & Minder, 1997).

RESULTS

Study selection

The systematic literature search was performed on 1/1/2015. This search resulted in 15057 citations. After removal of duplicates, 9204 single citations were examined on title and abstract. This procedure led to 1471 articles that were reviewed full text. A total of 44 studies met the inclusion criteria and were included in the meta-analyses. Figure 1 presents the study selection process.

Study characteristics

Table 1 presents the characteristics of the included studies. Forty-four studies and five companion papers with a total number of 6096 participants with depression evaluated the effects of psychotherapy compared to control groups at six months or longer post-randomization. Most of the included studies recruited their participants through clinical settings (n = 33) while nine studies recruited their participants through community samples and two studies used both clinical and community referrals. The included RCTs were conducted across twelve different countries: Australia, Brazil, China, Finland, Ireland, Norway, Spain, the Netherlands, the United Kingdom, the United States, Turkey and Uganda. All studies used all of the initially randomizedparticipants at the follow-up assessment. The follow-up duration varied from 6 to 18 months post-randomization. Most of the included studies did not report on the issue of out-of-protocol interval treatment during follow-up. Only four trials reported that participants were free to access treatment after the acute phase therapy (naturalistic follow-up; Table a, Appendix B1.)

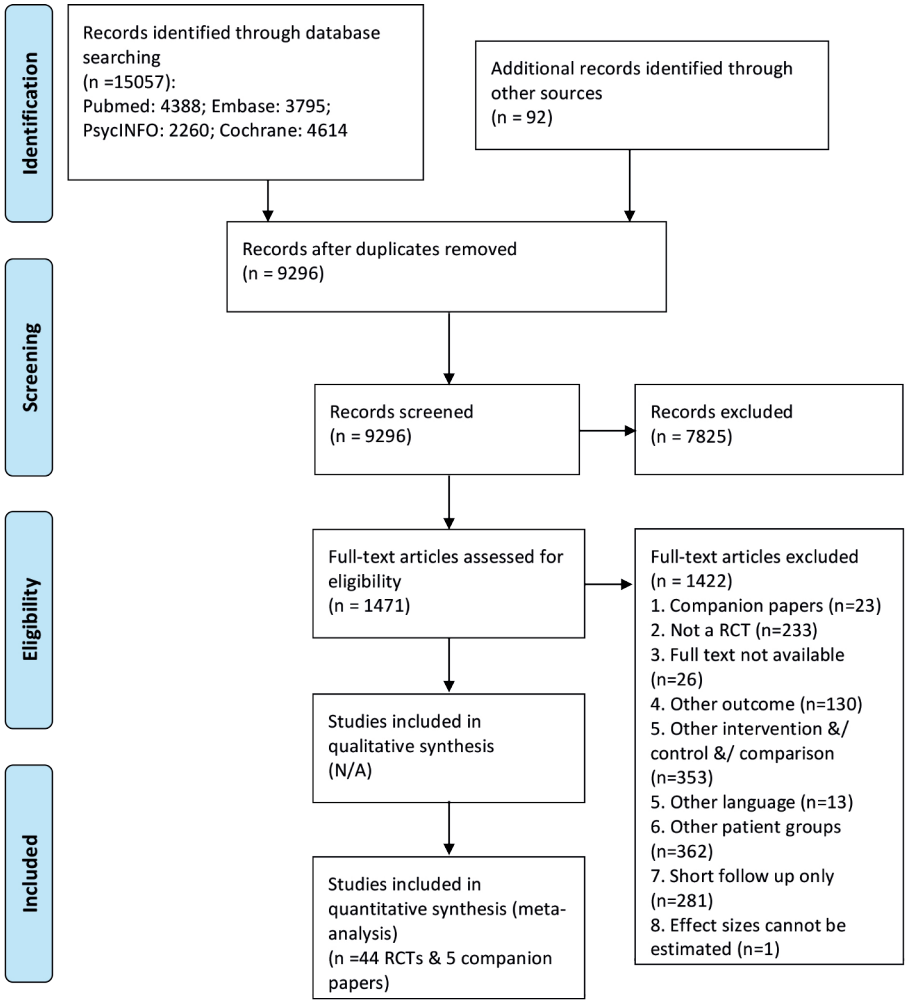

Figure 1. PRISMA flow chart of study selection process

Among the examined types of psychotherapy were behavioural activation, cognitive behavioural therapy, interpersonal psychotherapy, non-directive supportive therapy, problem solving therapy and psychodynamic therapy. We found no trials on long-term effects of social skills training. In the majority of the included studies, psychotherapy was administered face-to-face while six studies used web-based or telephoned based psychotherapy. The number of treatment sessions varied from 4 to 26 usually weekly sessions (more details on the duration of the therapy can be found in Table a., Appendix B1. Most of the included studies used treatment as usual (TAU) as the control comparison condition. The definition of TAU varied across different studies and countries. In the included trials TAU was mostly defined as therapy carried out by general practitioners (GPs), referrals to community mental health services and/or non-specific

antidepressant medications. Other types of control conditions were: attention controls, life style interventions, no further assessment, non-specific antidepressant medication, placebo alone or with clinical management, no treatment and waiting list (further details regarding the control conditions can be found in Table a., Appendix B)

Risk of bias of the included studies

The quality of the included studies varied. Most of the studies presented adequate random sequence generation (31/44) while the allocation was adequate in sixteen of the included RCTs. In the vast majority of the studies blinding of participants was not possible due to the nature of the psychotherapeutic interventions. However, one RCT used placebo psychotherapy. Finally, 26 studies used intention to treat analyses to handle incomplete outcome data and most of the studies were evaluated at a low risk for selective reporting (42/44) while all studies were free from other sources of bias (Figure 2).

Acute psychotherapy versus control conditions (at ≥ 6 months post randomizations)

All positive outcomes combined & quality of life

The results of all the meta-analyses are presented in Table 2. Forty-four studies (55 comparisons) compared psychotherapy to control groups at six months or longer post-randomization. Psychotherapy significantly outperformed control groups (OR = 1.92, $p < 0.001$). Heterogeneity was moderate (I^2: 65%, $p < 0.001$). The ORs and 95% CIs are presented in Figure 3. Visual inspection of Figure 3 suggested that two studies were outliers because the 95% confidence intervals around their effect sizes did not overlap with the 95% confidence intervals around the overall pooled effect size. Thus, we decided to exclude these two studies to examine the impact on heterogeneity. The resulting effect remained significant in favour of psychotherapy (OR = 1.65, $p < 0.001$), while the heterogeneity was reduced considerably to $I^2 = 20\%$ ($p > 0.05$). Due to this important reduction in heterogeneity, we decided to exclude these two studies from all further analyses. However, after the removal of the outliers, there was an indication for publication bias (see funnel plot a. in Appendix B2). In Duval and Tweedie's Trim and fill procedure the imputed point estimate changed to OR = 1.45 (95% CI: 1.27 to 1.67) after adjustment for publication bias, while Egger's test was significant ($p < 0.05$).

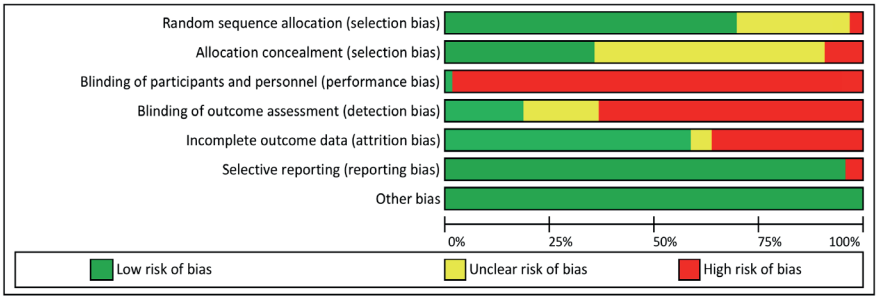

Figure 2. Risk of bias assessment

Table 1 – Characteristics of the included RCTs: psychotherapy (acute phase) vs. control groups in adults with depression

Studies	Diagnosis	Recruitment	Acute phase PT	N	N sessions	Continuation phase PT	Control group	N	FU (m)	Outcome	Country
Allart-van Dam, Hosman, Hoogduin, and Schaap (2007)	BDI ≥ 10	Com.	CBT	62	12	1	No treatment	41	12	DS (BDI)	NL
Bass et al. (2006)	MDD (DSM-IV)	Com.	IPT-G	107	16	No	TAU	117	6	DS (HSCL)	UG
Beeber et al. (2010)	CESD ≥ 16	Com.	IPT	39	16	No	TAU	41	6	DS (CESD)	US
Burns et al. (2013)	MDD (ICD-10)	Com.	CBT & TAU	18	12	No	TAU	18	8	DS (CISR), QoL (EQ-5D)	UK
Choi, Sirey, and Bruce (2013)	HAMD ≥ 15	CS	T-PST In person PST	43 42	6	6	Attention control	36	6	DS (HAMD)	US
Cooper, Murray, Wilson, and Romaniuk (2003)	MDD (SCID)	Com.	CBT DYN SUP	43 50 48	NR	No	TAU- GPs	52	18	DS (EPDS); Remission (SCID)	UK
Cramer, Salisbury, Conrad, Eldred, and Araya (2011)	Clinical Depression (PHQ-9 ≥ 10 and <21)	CS	CBT-G	52	12	2	TAU – GPs	21	6	DS (PHQ-9); Partial remission (PHQ-9<10); Response (50% PHQ-9)	UK
Dowrick et al. (2000)	MDE, DYS (ICD-10)	Com.	PST CBT	128 108	6 12	No	No treatment	189	6, 12	DS (BDI); QoL (SF-36)	FI, IE, NO, SP, UK
Duarte, Miyazaki, Blay, and Sesso (2009a)	MDD (DSM-IV)	CS	CBT	41	NR	6	TAU	44	9	DS (BDI)	BR
Dwight-Johnson et al. (2011)	PHQ-9 > 10	CS	Tele-CBT	50	8	No	Enhanced TAU	51	6	DS (PHQ-9); Response (50% PHQ-9)	US
Elkin et al. (1989); Shea et al. (1992)	MDD	CS	CBT IPT	59 61	16	No	Placebo & CM	62	18	Recovery (DSM-IV, RDC)	US
Evans and Connis (1995)	CESD ≥ 16	CS	CBT-G	29	8	No	No treatment	26	6	DS (CES-D)	US
Freedland et al. (2009)	MDD, Min DD (DSM-IV)	CS	CBT	41	12	No	TAU	40	6, 9	Remission (BDI< 7; HAMD < 7); Recovery (Sustain remission at FU); QoL (SF-36)	US

continued

Table 1 – Characteristics of the included RCTs: psychotherapy (acute phase) vs. control groups in adults with depression (continued)

Studies	Diagnosis	Recruitment	Acute phase PT	N	N sessions	Continuation phase PT	Control group	N	FU (m)	Outcome	Country
Gary, Dunbar, Higgins, Musselman, and Smith (2010)	MDD, Min DD (DSM-IV)	CS	CBT CBT & EX	19 18	12	If needed	TAU	17	6	DS (HAMD)	US
Geraedts, Kleiboer, Wiezer, van Mechelen, and Cuijpers (2014)	CESD ≥ 16	Com.	Web CBT	116	6	No	TAU	115	6, 12	DS (CESD)	NL
Hamamci et al. 2016	BDI ≥ 19	Com.	CBT-G CBT-G & PD	10 10	11 11	No	No treatment	11	6	DS (BDI)	TR
Honey, Bennett, and Morgan (2002)	EPD > 12	CS	SUP-G	23	8	No	TAU	22	6	DS (EPD); Partial remission (EPD < 13)	UK
Kay-Lambkin, Baker, Lewin, and Carr (2009)	MDD (DSM-IV)	CS & com.	In person CBT C-CBT	35 32	10 9	No	No treatment	30	6, 12	DS (BDI)	UK
Kessler et al. (2009)	MDD (ICD-10)	CS	CBT	149	10	No	WL	148	8	Remission (BDI<10); QoL (EQ-5D)	UK
King et al. (2000)	BDI ≥ 14	CS	SUP CBT	67 63	12	No	TAU	67	12	DS (BDI), QoL (EQ-5D)	UK
Laidlaw et al. (2008)	MDD (DSM-IV)	CS	CBT	21	17	No	TAU	23	6	DS (BDI, HAMD)	UK
Lamers et al. (2010)	Min, mild, mod. DD (DSM-IV)	CS	CBT & self management	183	10	No	TAU	178	9	DS (BDI); QoL (SF-36)	NL
Lustman, Griffith, Freedland, Kissel, and Clouse (1998)	MDD (DSM-III)	CS	CBT	25	10	No	Non specific ADM	26	6	Response (50% BDI); Remission (BDI <10)	US
MacPherson et al. (2013)	BDI-II ≥ 20	CS	SUP	302	12	No	TAU	151	12	DS (BDI-II, PHQ-9)	UK
Jeanne Miranda et al. (2003); J. Miranda et al. (2006)	MDD (ICD-10)	CS	CBT	90	8	No	TAU	89	12	Remission (HAMD < 7)	US

continued

Table 1 – Characteristics of the included RCTs: psychotherapy (acute phase) vs. control groups in adults with depression (continued)

Studies	Diagnosis	Recruitment	Acute phase PT	N	N sessions	Continuation phase PT	Control group	N	FU (m)	Outcome	Country
Mohr, Carmody, Erickson, Jin, and Leader (2011)	MDD (DSM-IV)	CS	Tele-CBT	41	16	No	TAU	44	6	DS (HAMD, PHQ-9)	US
Mossey, Knott, Higgins, and Talerico (1996)	GDS > 10	CS	SUP	31	10	No	TAU	38	6	DS (GDS)	US
O'Mahen, Himle, Fedock, Henshaw, and Flynn (2013)	MDD (DSM-IV)	CS	CBT	30	12	No	TAU	25	6	DS (BDI); Partial remission (BDI <14)	US
Pagoto et al. (2013)	MDD (DSM-IV)	CS & com.	BA	78	26	No	LI	83	6, 12	Remission (BDI < 10, HRSD < 7)	US
Poleshuck et al. (2014)	HRSD>15	CS	IPT	34	8	No	TAU	28	6,9	DS (BDI, HRSD)	US
Power and Freeman (2012)	MDD (DSM-IV)	CS	CBT IPT	39 22	16	No	TAU	10	6	DS (BDI)	UK
Prendergast and Austin (2001)	EPDS ≥ 12	CS	CBT	17	6	No	TAU	20	6	DS (EPDS)	AU
Qiu, Chen, Gao, Xu, Tong, Yeng, et al. (2013)	MDD (DSM-IV)	CS	CBT-G	31	10	No	WL	31	6	DS (HRSD)	CN
Scott, Tacchi, Jones, and Scott (1997)	MDD (DSM-III-R)	CS	CBT	24	6	No	TAU	24	8, 14	DS (BDI, HRSD)	UK
Serfaty et al. (2011); Serfaty et al. (2009)	BDI-II ≥ 14	CS	CBT & TAU	70	12	No	TAU	67	10	DS (BDI-II); QoL (EQ-5D)	UK
Simpson, Corney, and Beecham (2003)	BDI ≥ 14	CS	DYN	92	6-12	No	TAU	89	6, 12	DS (BDI); Partial remission (BDI <14)	UK
Smit et al. (2006)	MDD (DSM –IV)	CS	CBT & DRP	44	10-12	No	TAU	72	6	Remission (DSM-IV); Recovery (DSM-IV)	NL
Swartz et al. (2008)	MDD (DSM-IV)	CS	IPT	26	8	No	TAU	21	9	DS (BDI, HRDS)	US
Tandon, Leis, Mendelson, Perry, and Kemp (2014)	CESD ≥ 16	CS	CBT-G	61	6	No	TAU	59	6	DS (BDI-II)	US

continued

Table 1 – Characteristics of the included RCTs: psychotherapy (acute phase) vs. control groups in adults with depression (continued)

Studies	Diagnosis	Recruitment	Acute phase PT	N	N sessions	Continuation phase PT	Control group	N	FU (m)	Outcome	Country
Teasdale, Fennell, Hibbert, and Amies (1984)	MDD (RDC)	CS	CBT	17	20	2	TAU	17	6	DS (BDI)	US
Bosmans, van Schaik, et al. (2007); van Schaik et al. (2006)	MDD (PRIME-MD)	CS	IPT	69	10	No	TAU	74	12	DS (GDS-15, MADRS); Partial remission (MADRS<10); Response (50% MADRS); Recovery (PRIME-MD); QoL (SF-36)	NL
Verduyn, Barrowclough, Roberts, Tarrier, and Harrington (2003)	BDI ≥ 15	Com.	CBT-G	47	16	No	No treatment Placebo PT	28 44	6, 12	DS (BDI, HAMD)	UK
Wiles et al. (2013)	MDD (ICD-10)	CS	CBT & TAU	234	12	6	TAU	235	12	DS (BDI); Response (50% BDI); Remission (BDI < 10); QoL (SF-12)	UK
Williams, Wilson Morrison, McMahon, Andrew, and Allan (2013)	BDI-II ≥ 14	CS	Web CBT	141	3	No	TAU	140	12	DS (BDI-II)	UK

Abbreviations: ADM: Antidepressant medication ACT: Acceptance and Commitment Therapy; BA: Behavioural Activation therapy; BDI: Beck Depression Inventory; BR: Brazil; C-CT: Computerized Cognitive Therapy; CBT & EX: Combined Exercise and Cognitive Behavioural Therapy; CH: Switzerland; CISR: Clinical Interview Schedule Revised; CM: Clinical Management; CN: China; Com: Community sample; CS: Clinical Sample CT: Cognitive Therapy; DRP: Depression Recurrence Prevention; DS: Depression Severity; DSM: Diagnostic and Statistical Manual of Mental Disorders; DYN: Psychodynamic therapy; DYS: Dysthymia; EPDS: Edinburg Postnatal Depression Scale; EQ-5D: EuroQol- 5 Dimensions; FACT-B: Functional Assessment of Cancer Therapy-Breast; FACT-B: Functional Assessment of Cancer Therapy-Breast; FI: Finland; G: Group therapy; GDS: Geriatric Depression Scale; HRSD: Hamilton Rating Scale for Depression; HSCL: Hopkins Symptoms Checklist; ICD-10: International Classification of Diseases; IE: Ireland; IPT: Interpersonal Psychotherapy; LI: Lifestyle Intervention; m: months; MADRS: Montgomery Asberg Depression Rating Scale; MBCT: Mindfulness Based Cognitive Therapy; MDD: Major Depressive Disorder; MDE: Major Depressive Episode; MinDD: Minor Depressive Disorder; Mod. DD: Moderate depressive disorder; N: Number; NL: The Netherlands; NO: Norway; NR: Not Reported; PD: integrated Psychodrama; PHQ-9: Patient Health Questionnaire; PST: Problem Solving Therapy; PT: Psychotherapy; QoL: Quality of Life; RDC: Research Diagnostic Criteria; SCID: Structural Clinical Interview for DSM disorders; SCL-20: Symptom Checklist-20; SE: Sweden; SF: Short Form health survey; SP: Spain; SS-G: Social Support – Group therapy; SSM: Supportive Stress Management; SUP: Non directive Supportive therapy; TAU: Treatment As Usual; Tele: Telephone; TR: Turkey; TR: Turkey; UG: Uganda; UK: the United Kingdom; US: the United States; WHOQOL: World Health Organization Quality of Life; WL: Waiting List

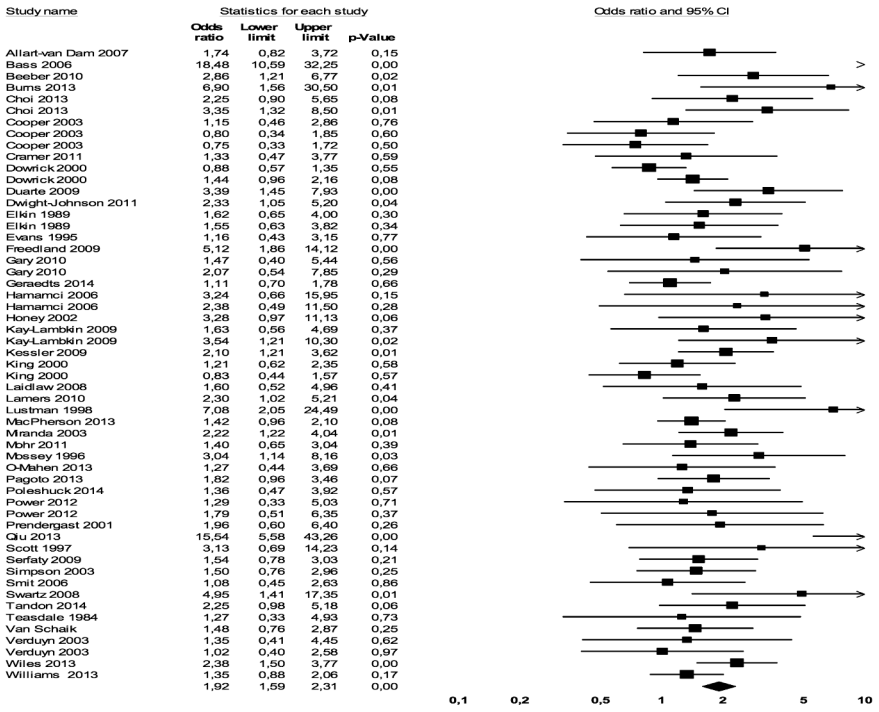

Figure 3. Forest plot of all positive outcomes combined.

In seven included studies, acute phase psychotherapy was followed by booster sessions. These sessions were provided in the event that some patients needed further treatment. Considering that this type of continuation psychotherapy might have influenced the maintenance outcomes of psychotherapy, we decided to exclude these trials in a sensitivity analysis. The results of this analysis (44 comparisons) indicated that psychotherapy significantly outperformed control groups at 6 months or longer post randomization (OR = 1.58, $p < 0.05$). However, Duval and Tweedie's Trim and fill procedure resulted in an adjusted OR of 1.39 (95% CI: 1.19 to 1.62) and Egger's test was significant ($p < 0.05$) (see also funnel plot b. in Appendix B2)

In order to examine possible sources of heterogeneity, we conducted a series of subgroup analyses (Table 2). We found significant differences between subgroup of studies that were specifically targeted at individuals with MDD (diagnosed by a clinical interview) and studies that recruited individuals who scored high on self-report outcome measures ($p < 0.05$). Subgroup analysis also revealed a significant difference between the studies that provided booster sessions after the completion of therapy, and studies that provided no additional sessions ($p < 0.05$). Other subgroup analyses did not result in significant differences. Moreover, we conducted meta-regression analyses to examine the associations between the dependent variable "all positive outcomes combined" and the independent variables "number of sessions" and "follow-

up duration". Results indicated that the effect of psychotherapy significantly decreased as the follow-up duration increased (slope: -0.07, 95% CI: -0.10 to -0.04, $p < 0.001$; Figure 4). No significant association was found between response to treatment and number of sessions (slope: 0.001, 95% CI: -0.02 to 0.03, $p > 0.05$).

With regards to quality of life, psychotherapy resulted in a significantly better quality of life compared to control groups at ≥ six months post-randomization across the eight studies that examined this outcome (Hedges's g = 0.22, 95% CI: 0.11 to 0.32, $p < 0.001$; Figure 5). Heterogeneity was zero (95% CI: 0% to 68%, $p < 0.001$)

Recovery, remission, partial remission and response

Separate meta-analyses were conducted for recovery, remission, partial remission and response rates at six months or longer post-randomization. Recovery was reported in five comparisons between psychotherapy and control groups. Psychotherapy outperformed control conditions (OR = 1.77, $p < 0.05$). Similar long-term effects were observed for remission across ten comparisons. Psychotherapy resulted in higher remission rates compared to control groups (OR = 1.70, $p < 0.05$) Heterogeneity was moderate. Partial remission was examined across nine comparisons. Psychotherapy outperformed control groups on partial remission rates (OR = 1.61, $p < 0.05$). Heterogeneity was low. There was a small indication for publication bias (see funnel plot c in Appendix B2). Using the trim and fill procedure, the imputed OR was 1.51 ($p < 0.05$), however, Egger's test was not significant. Finally, response rates were examined across 5 comparisons. Psychotherapy resulted in significantly higher response rates compared to controls (OR = 2.06, $p < 0.001$) and the heterogeneity was low.

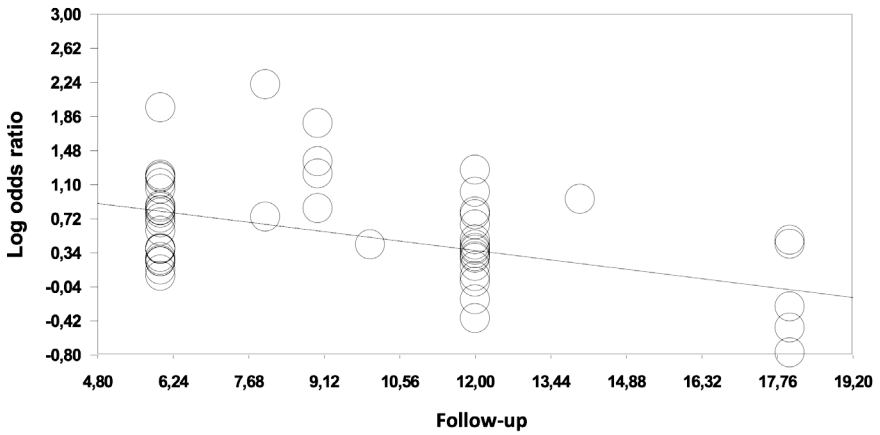

Figure 4. Meta-regression analysis of the association between follow-up duration and treatment outcome

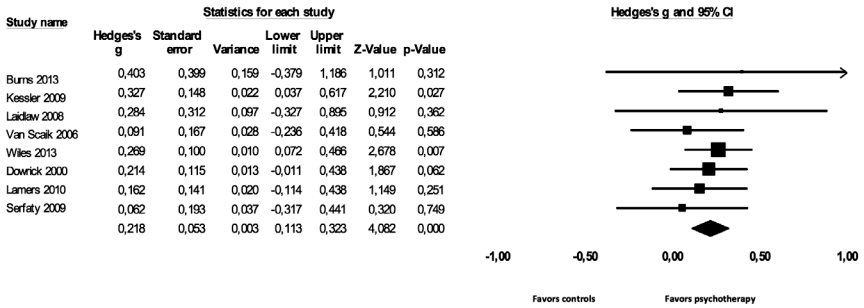

Figure 5 Forest plot of quality of life

Long term effects of individual psychotherapies

We conducted separate meta-analyses for each type of psychotherapy when three or more studies were available. If less than three studies were available, results were described narratively. The outcomes of the individual comparisons are presented in Table 2. CBT resulted in a significantly higher positive therapy outcomes compared to control groups across thirty-six comparisons (OR = 1.70, $p < 0.001$). Heterogeneity was low. However, using Duval and Tweedie's Trim and fill procedure the values changed to OR = 1.51 (95% CI 1.27 to 1.79), while Egger's test was significant ($p < 0.05$) (see also funnel plot d. in Appendix B2). IPT outperformed control groups on all positive outcomes combined (OR = 1.90, $p < 0.05$) across six comparisons. Heterogeneity was zero. SUP did not result in significant long-term differences compared to control conditions in all positive outcomes combined (five comparisons). PST resulted in higher positive outcomes rates compared to controls at six months or longer post-randomization (OR = 1.91, $p < 0.05$) across three comparisons. Only one study was found on long-term effects of DYN therapy. Simpson et al. 2003 reported that DYN therapy significantly outperformed control groups in partial remission rates at 6 months follow up. Finally, we found one study examining the long-term effects of BA. Pagoto et al (2013) found that BA resulted in higher remission and response rates compared to light intervention group at 6 months follow up.

DISCUSSION

To the best of our knowledge this is the first systematic review examining the long-term effects of acute phase psychotherapy compared to control groups in adults with depression. Our hypothesis that psychotherapy would outperform the control groups on all-positive outcomes combined (recovery, remission, partial remission, response and reduction in depression severity) and on quality of life was confirmed at a follow-up of six months or longer. This conclusion was replicated by analysing each type of dichotomous outcome separately. Additionally, we examined the effects of different types of psychotherapy individually and the results showed that treatment gains were maintained through six months or longer post-randomization across all types of psychotherapy with the exception of non-directive supportive treatment,

Table 2 Long-term effects of psychotherapy in adults with depression compared to control groups (at ≥ 6 months post-randomization)

All types of psychotherapy vs. controls		N	OR	95%CI	I^2	95%CI	P
All positive outcomes combined		55	1.92	1.60 to 2.31	65	53 to 74	0.000
All positive outcomes combined (two outliers excluded)		53	1.65	1.46 to 1.87	20	0 to 43	0.000
All positive outcomes combined (psychotherapy with booster sessions excluded)		44	1.58	1.38 to 1.81	22	0 to 66	0.000
Recovery		5	1.74	1.09 to 2.75	30	0 to 73	0.025
Remission		10	1.70	1.20 to 2.45	57	14 to 79	0.003
Partial remission		9	1.61	1.16 to 2.22	3	0 to 66	0.004
Response		7	2.06	1.53 to 2.80	19	0 to 63	0.000
CBT vs. controls							
All positive outcomes combined		36	1.70	1.45 to1.98	18	0 to 46	0.000
IPT vs. controls							
All positive outcomes combined		6	1.90	1.30 to 2.77	0	0 to 75	0.001
SUP vs. controls							
All positive outcomes combined		5	1.39	0.86 to 2.24	52	0 to 83	0.181
PST vs. controls							
All positive outcomes combined		3	1.91	1.16 to 3.15	34	0 to 78	0.011
Sub-groups – all positive outcomes combined							
CBT	CBT vs.	36	1.70	1.45 to1.98	18	0 to 46	0.60
	Other PT	17	1.58	1.29 to 1.96	25	0 to 58	
IPT	IPT vs.	6	1.90	1.30 to 2.77	0	0 to 75	0.46
	Other PT	47	1.63	1.43 to 1.86	23	0 to 47	
SUP	SUP vs.	6	1.90	1.30 to 2.77	0	0 to 75	0.44
	Other PT	48	1.69	1.48 to 1.91	14	0 to 40	
PST	PST vs.	3	1.91	1.16 to 3.15	34	0 to 78	0.56
	Other PT	50	1.64	1.44 to 1.87	20	0 to 44	
Control group	TAU vs.	37	1.65	1.43 to 1.90	16	0 to 44	0.84
	Other	16	1.70	1.32 to 2.18	31	0 to 62	
Diagnosis	MDD vs.	25	1.88	1.53 to 2.31	26	0 to 55	0.04
	Other	28	1.45	1.27 to 1.66	0	0 to 42	
Sub-groups – all positive outcomes combined							
Quality of studies	High (defined as low scores in ≥ 4 items) vs.	32	1.56	1.33 to 1.82	31	0 to 56	0.15
	Low quality studies	21	1.88	1.53 to 2.32	0	0 to 47	
Recruitment	Community vs.	17	1.40	1.11 to 1.75	28	0 to 60	0.07
	Clinical sample	36	1.78	1.56 to 2.03	3	0 to 40	
Target group	Older adults vs.	7	1.99	1.42 to 2.78	0	0 to 71	
	Post-partum vs.	8	1.53	0.96 to 2.43	41	0 to 74	0.51
	Other	38	1.63	1.42 to 1.87	21	0 to 47	
Therapy continuation	Booster sessions vs.	9	2.21	1.67 to 2.91	0	0 to 65	
	No further continuation of the therapy	44	1.58	1.38 to 1.81	22	0 to 46	0.03
Treatment format	Individual vs.	44	1.63	1.43 to 1.87	25	0 to 49	0.46
	Group format	9	1.88	1.32 to 2.67	0	0 to 46	
Type of therapy	BA vs.	1	1.8	0.96 to 3.45	NA	NA	
	CBT vs.	36	1.70	1.45 to1.98	18	0 to 46	
	DYN vs.	2	1.10	0.56 to 2.16	36	NA	0.73
	IPT vs.	6	1.90	1.30 to 2.77	0	0 to 75	
	PST vs.	3	1.91	1.16 to 3.15	34	0 to 78	
	SUP	6	1.90	1.30 to 2.77	0	0 to 75	

Abbreviations: BA: Behavioural Activation; CBT: Cognitive Behavioural Therapy; CI: Confidence Intervals; DYN: Psychodynamic psychotherapy; IPT: Interpersonal Psychotherapy; IPT: Interpersonal Psychotherapy; MDD: Major Depressive Disorder; N: Number of comparisons; OR: Odds Ratio; PST: Problem Solving Therapy; PT: Psychotherapy; SUP: non-directive supportive therapy TAU: Treatment As Usual

which was found to be less efficacious. We also found that in the long-term, psychotherapy resulted in higher effects compared to control groups when it was provided with additional booster sessions, or when it was exclusively targeted at adults with MDD. Finally, the results of this systematic review indicated that as the follow-up progressively increased the effects of psychotherapy vs. control decreased.

Our findings are in line with previous work of Piet and Hougaard (2011) and Biesheuvel Biesheuvel-Leliefeld et al. (2015). Piet and Hougaard (2011) found a relative risk reduction of 34% in favour of maintenance mindfulness-based cognitive therapy compared to treatment as usual or pill placebo at six months or longer post-randomization in patients with MDD. Moreover, Biesheuvel-Leliefeld et al. (2015) found that maintenance psychotherapy reduced significantly the risk of relapse in patients with MDD. To our knowledge there is no other systematic review on the long-term effects of acute phase psychotherapy. Moreover, the finding that different types of psychotherapy, with the exception of non-directive supportive therapy, result in similar effects in treating depression is consistent with the meta-analyses of direct comparisons of different types of psychotherapy conducted by Cuijpers, van Straten, Andersson, and van Oppen (2008b) and Barth et al. (2013). These meta-analyses showed no significant difference between the effects of seven major types of psychotherapy in treating depression and that non-directive supportive therapy is less efficacious compared to other types of psychotherapy. It should be noted at this point that although we analysed and described different types of psychotherapy separately, the interpretation of the findings has to be done with caution as the majority of the included RCTs used CBT as a psychotherapy intervention.

We observed a decreasing difference between psychotherapy and control conditions over length of follow-up. The reasons for this reduction vary among the examined trials. In certain instances, this decrease in effects is due to greater relapse rates in the psychotherapy groups as the effects of acute treatment waned. However, in the majority of instances, this decrease in effects in the course of time can be attributed to spontaneous remission rates experienced by patients in the control groups. This is in line with research findings suggesting that approximately half of the untreated patients who are diagnosed with major depression will experience spontaneous remission within a year (Driessen, Cuijpers, Hollon, & Dekker, 2010).

The finding that studies required a diagnosis of major depression presented larger psychotherapy long-term differences compared to studies that used elevated depressive symptoms as inclusion criterion, is consistent with previous research findings regarding the moderating effects of depression severity in treatment outcome. The meta-analysis of Driessen, Cuijpers, Hollon, et al. (2010) showed that psychotherapy might be more efficacious for more severely depressed individuals. Furthermore, Bower et al. (2013) conducted an individual patient data meta-analysis to examine the influence of baseline depression severity on the effects of low intensity psychotherapeutic intervention in outpatients with depression. The authors found that patients who had more severe depressive symptoms at baseline showed greater treatment effects in

comparison with patients who had less severe symptoms of depression at the intake (Bower et al., 2013).

The present study addresses, for the first time, the long-term effects of psychotherapy on quality of life. However, a recent systematic review by Kolovos, Kleiboer, and Cuijpers (2016) came to similar conclusions regarding the short-term effects of psychotherapy on quality of life. The authors meta-analysed the effects of forty-four RCTs on global quality of life, mental and physical components and found that psychotherapy has a positive impact on the quality of life at the post-treatment assessment (Kolovos et al., 2016).

The present study has several limitations. Firstly, treatment as usual was the most common control group used by the included studies. However, this condition had in some cases unclear definitions and generally presented important variations across countries. We also observed moderate heterogeneity between studies as a result of two outliers and thus, these studies were excluded in any further analyses. This difference, between the two studies and the rest studies of our sample, may have been caused by differences in populations or by differences in the control conditions. The study by Bass et al. (2006) was conducted in Uganda and the study of Qiu, Chen, Gao, Xu, Tong, Yeng, et al. (2013) was conducted in China, while the great majority of the rest-included studies were conducted in western countries. Thus, cultural differences may account for the observed differences between these two studies and the rest of the studies in our sample. Further, we observed some indications for publication bias in our main comparison between psychotherapy and control groups. However, the superior effects of psychotherapy remained significant after adjustment for publication bias. The lower effect size estimate of low quality studies was not significantly different from high quality studies. Finally, the external validity of the present meta-analysis might be limited due to the design of the included studies. A common difficulty of the RCT design is the limited duration of the provided treatment. For instance, the vast majority of the included trials did not provide booster sessions after acute phase treatment. In contrast, therapists in clinical practice often provide continuation and maintenance therapy to recently improved patients. Thus the literature under examination represents a special case of a particular research design for psychotherapy.

Future research should examine ways to maintain the positive effects of psychotherapy during a more extensive follow-up period. Additionally, maintenance psychotherapy could be employed in order to sustain treatment response as the follow-up duration progressively increases. Studies should address the efficacy of different types of psychotherapy, in order to provide enough power to analyse the effects of each type of intervention separately. It is also important to address questions regarding predictors and moderators to treatment outcomes on long-term follow-up. This will provide us with essential information on who may benefit the most from psychotherapy over time. This need should drive new meta-analytic approaches such as individual patient data meta-analysis. Furthermore, more research is needed to address long-term effects of psychotherapy compared to pharmacotherapy, as well as the effects of combined psychotherapy and pharmacotherapy treatment. This would provide us with

important information regarding the optimal therapeutic approach with respect to the long-term outcome of adult depression treatment.

In conclusion, acute phase psychological interventions appear promising in treating depression in the long-term. The improvement in depressive outcomes, while less apparent as the follow up duration increased, was considerable. Given the chronicity and disability associated with depression, these findings should be taken into account in clinical and policy decision-making. Currently, pharmacotherapy is the predominant treatment for depression with more and more patients being prescribed with antidepressant medications in mental health care services worldwide. However, concerns have arisen about the side effects of antidepressants and about the durability of their effects after discontinuation. The results of the present meta-analysis recommend that psychological interventions may offer a viable approach to improve long-term outcomes of depression care. In light of these therapeutic gains, psychotherapy should be available in primary and secondary mental health care. Patients with depression should be able to discuss psychological treatment options with their doctors and decide based on their preferences. Alternative treatment modalities, such as maintenance psychotherapy or the combination of psychotherapy and pharmacotherapy should also be considered to sustain long-term benefits.

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02

CHAPTER 3

COMBINING PHARMACOTHERAPY AND PSYCHOTHERAPY OR MONOTHERAPY FOR MAJOR DEPRESSION?

A META-ANALYSIS ON THE LONG-TERM EFFECTS

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de Beurs, D., & Cuijpers, P. (2016)

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ABSTRACT

Background:
The present meta-analysis aimed to examine to what extent combined pharmacotherapy with psychotherapy results in a different response to treatment compared to psychotherapy or pharmacotherapy alone in adults with major depression at six months or longer post-randomization.

Methods:
A systematic literature search resulted in 23 randomized controlled trials with 2184 participants. Combined treatment was compared to either psychotherapy or anti-depressant medication alone in both the acute phase and the maintenance phase. Odds ratios of a positive outcome were calculated for all comparisons.

Results:
In acute phase treatment, combined psychotherapy with antidepressants outperformed antidepressants alone at six months or longer post randomization in patients with major depressive disorder (OR = 2.93, 95%CI 2.15 to 3.99, $p < 0.001$). Heterogeneity was zero (95%CI 0 to 57%, $p > 0.05$). However, combined therapy resulted in equal response to treatment compared to psychotherapy alone at six months or longer post randomization. As for the maintenance treatment, combined maintenance psychotherapy with antidepressants resulted in better-sustained treatment response compared to antidepressants at six months or longer post randomization (OR = 1.61, 95%CI 1.14 to 2.27, $p < 0.05$). Heterogeneity was zero (95%CI 0 to 68%, $p > 0.05$).

Conclusions:
Combined therapy results in a superior enduring effect compared to antidepressants alone in patients with major depression. Psychotherapy is an adequate alternative for combined treatment in the acute phase as it is as effective as combined treatment in the long-term.

INTRODUCTION

Depression is a highly prevalent disorder and one of the leading causes of disability worldwide. According to the World Health Organization (WHO), depression is currently the fourth largest contributor to the global burden of disease and is expected to become the second cause of disability by 2020. This is a result of the recurrent nature of depression and its excessive economic costs, mortality, and morbidity rates (Reddy, 2010). Therefore, it is crucial for clinical decision making to identify which therapeutic strategies should be employed to produce the most favorable outcome in the treatment of depression in both the short and the long term.

There is ample evidence for the short-term effects of psychotherapies and pharmacological treatments for depression in the acute (aimed at alleviating the symptoms of an active depression) and the maintenance phase (aimed at preventing future recurrence of the depressive disorder) (Akechi, Okuyama, Onishi, Morita, & Furukawa Toshi, 2008; Beltman, Voshaar, & Speckens, 2010; Casacalenda, Perry, & Looper, 2002; Cuijpers, Andersson, Donker, & van Straten, 2011; Cuijpers & Dekker, 2005; Dennis, Ross, & Grigoriadis, 2007; Kennedy, 2013; Pizzi et al., 2011; Williams et al., 2000). Meta-analytic studies have shown that, at post-treatment, the effects of psychotherapy and pharmacotherapy in treating mild to moderate depression are comparable (Cuijpers et al., 2013; Cuijpers, van Straten, van Oppen, & Andersson, 2008), with a combination of pharmacotherapy and psychotherapy showing the best treatment effects when compared to pill placebo, pharmacotherapy and psychotherapy alone (Cuijpers & Dekker, 2005; Cuijpers, Dekker, Hollon, & Andersson, 2009; Cuijpers, Reynolds, et al., 2012; Cuijpers et al., 2014; Khan, Faucett, Lichtenberg, Kirsch, & Brown, 2012; Pampallona, Bollini, Tibaldi, Kupelnick, & Munizza, 2004). However, the long-term effects of the combination of psychotherapy and pharmacotherapy are not well known.

Cuijpers, van Straten, Warmerdam, and Andersson (2009) conducted a meta-analysis to examine the effects of combined psychotherapy with pharmacotherapy versus psychotherapy alone. The authors found no differences in the effects between combined treatment and psychotherapy in the follow up in patients with depression. However, Cuijpers, van Straten, et al. (2009) also included short time intervals in their definition of long-term outcomes, e.g., 1 month follow up (Cuijpers, van Straten, et al., 2009). Thus, an examination focusing specifically on longer follow up periods is warranted. Barber, Muran, McCarthy, and Keefe (2013) conducted a systematic review to examine the absolute and relative efficacy of dynamic therapy in treating several mental disorders, such as depression and anxiety. The authors reported that dynamic therapy in combination with pharmacotherapy resulted in significantly higher remission rates compared to pharmacotherapy alone in adults with depression in the long-term (Barber et al., 2013). However, the number of included studies was small (n=3) and the results cannot be generalized to other types of psychotherapy. To our knowledge, no systematic review has examined the effects of combined treatment of all major types of psychotherapy and pharmacotherapy against pharmacotherapy alone in adults with major depressive disorder (MDD) in the long term.

Existing treatment guidelines recommend that the provision of antidepressant treatment should last for at least six months in order to prevent recurrence (American Psychiatric Association, 2000). Thus, it is essential to further examine the effects of combined therapy in the long term; such knowledge will provide insight into which therapy we should consider as first line treatment for major depression. The present meta-analysis aimed to examine to what extent combined pharmacotherapy with psychotherapy results in a different response to treatment compared to psychotherapy and pharmacotherapy alone in adults with major depression at six months or longer post-randomization.

METHODS

This study is based on a more extensive report for the development of treatment guidelines on the long-term effects of psychotherapy on depression: Karyotaki, E., Smit, Y., Cuijpers, P., Gillain, B., Fairon, N., Paulus, D., Robays, J., Holdt Henningsen, K. (2014). Major Depression: Long term efficacy of psychotherapy, alone or in combination with antidepressants. KCE Reports.

Search strategy

We conducted a systematic literature search in the bibliographic databases of Medline, PsycInfo, Embase and the Cochrane library from database inception to September 1, 2014. Detailed search strategies for PubMed are given in Appendix A. This strategy was combined with a filter for systematic reviews provided by PubMed and a filter for RCTs as recommended in the Cochrane Handbook (Higgins & Green, 2011). Search strategies for other databases were built accordingly.

In addition to the systematic literature search, we checked the references of the selected studies as well as other systematic reviews and meta-analyses in order to identify additional relevant studies. Moreover, we checked an existing database of randomized trials on psychotherapy for depression that has been used by several meta-analyses and is updated yearly (Cuijpers, van Straten, Warmerdam, et al., 2008).

After removal of duplicate publications, two researchers (EK and YS or DB supervised by PC) independently examined titles and abstracts to remove records that were obviously not relevant to the research question according to the guidelines of the Cochrane Handbook (Higgins & Green, 2011). Studies that possibly met inclusion criteria were retrieved full-text and were examined by the same two researchers independently. Any disagreement regarding the inclusion was solved through discussion, and if needed, the opinion of a third researcher (PC) was sought.

Study selection

We included all main psychotherapy interventions that have been identified in an expert taxonomy of psychotherapy for adult (≥ 18 years of age) depression (Cuijpers, van Straten, Warmerdam, et al., 2008). Here, psychotherapy was classified into seven different types: behavioral activation, cognitive-behavioral therapy, interpersonal therapy, problem solving

therapy, psychodynamic therapy, social skills training, and supportive counseling. Operational definitions of each type of psychotherapy are given elsewhere (Cuijpers, van Straten, Warmerdam, et al., 2008). We considered for inclusion acute phase treatments as well as maintenance treatments (definitions are given in table 1) and distinguished these throughout the analyses. The selected interventions were main psychotherapy interventions combined with antidepressive agents compared to main psychotherapy intervention or antidepressants alone.

Table 1. Definitions

Psychotherapy	Psychotherapy was defined as an intervention in which verbal communication between a therapist and a patient is the core element, or in which a psychological treatment is contained in book format (bibliotherapy) or electronic format (internet-based treatment) that the patient works through more or less independently, but with some kind of personal support from a therapist (guided by telephone, e-mail, or otherwise) (19)
Acute phase treatment	Therapy during the occurrence of depressive symptoms that is targeted at alleviating the symptoms of an active major depressive episode
Maintenance treatment	Therapy in which patients receive maintenance treatment sessions at low frequency rates, for example once monthly, and is aimed at preventing future recurrences of major depressive episode

The primary outcomes of the present meta-analysis were treatment response and sustained response. Treatment response was defined as every positive outcome achieved, such as whether a patient met criteria for remission or was free from relapse or recurrence. Moreover, sustained response was defined as a treatment response that was continued during and after maintenance treatment. Other outcomes were condition-related outcomes (depression rating scales).

Only outcomes at six months or longer after randomization were considered for inclusion. This cut off was chosen because remission is defined as the absence of a depressive disorder three months after the end of therapy, and because anti-depressant medication needs to be provided for at least six months (American Psychiatric Association, 2000). Additionally, a later time point for the cut off did not seem feasible as few studies have a longer follow up period. Outcomes were extracted for different time periods (six months and one year or longer).

Quality assessment

Two reviewers assessed study quality independently (EK and YS) based on the criteria of the Cochrane Risk of Bias tool (Higgins and Green, 2011). Disagreement was resolved through discussion and, if needed, the opinion of a third researcher (PC) was sought.

Data extraction

The following data were extracted from the included RCTs: patient characteristics, type of psychotherapy, treatment format, number of treatment sessions, type of pharmacotherapy, type of control and data on the follow up period. In some studies, outcome data were only reported

for patients who responded to treatment in the acute treatment phase, while others report outcomes for the full, intention-to-treat sample. When available, intention-to-treat data were selected. One reviewer (EK) extracted data; a second reviewer (PC) checked the extracted data.

Description of the analysis

The primary focus was on dichotomous outcomes. We calculated for each comparison the odds ratio (OR) of a positive outcome, based on dichotomous results, such as remission and response, or the proportion of patients that no longer met criteria for a depressive disorder according to a diagnostic interview. The OR shows the odds that an event (e.g. treatment response) will occur in the treatment group (e.g. combined therapy) compared to the odds of the same event occurring in the control group (e.g. psychotherapy or antidepressants alone). An OR > 1 increases the odds that an event will occur in the treatment group. Reversely, an OR < 1 decreases the odds that an event will occur in the treatment group (Deeks et al., 2008). Generally, an OR of 1.5 is considered a small effect size, while an OR of 2.5 and OR of 4 represents a medium and a high effect size respectively (Rosenthal, 1996).

Where more than one dichotomous outcome was reported, we calculated the mean of the effect sizes according to Borenstein, Hedges, Higgins, and Rothstein (2009) procedures. Thus, each comparison resulted in only one effect. If no dichotomous outcomes were reported, the standardized mean difference (SMD) was calculated as the difference in mean scores divided by the pooled standard deviation. The SMD was converted into the OR according to the procedures given by Borenstein et al. (2009). For dichotomous outcomes all randomized patients were taken as the denominator, and reported outcomes in completers were taken as the numerator. To calculate pooled relative risks, we used the computer program Comprehensive Meta-Analysis (version 2.2.021). Because we expected considerable heterogeneity among the studies, we used the random effects model in order to pool the studies.

Heterogeneity

As a test of homogeneity of effect sizes, the I2-statistic was calculated which is an indicator of heterogeneity in percentages. A value of 0% indicates no observed heterogeneity, and larger values indicate increasing heterogeneity, with 25% as low, 50% as moderate, and 75% as high heterogeneity (Higgins, Thompson, Deeks, & Altman, 2003). 95% confidence intervals (CI) were calculated around I2 (Ioannidis, Patsopoulos, & Evangelou, 2007) using the non-central chi-squared-based approach within the heterogi module for Stata (Orsini, Bottai, Higgins, & Buchan, 2005). The Q-statistic was calculated, and reported when significant.

Additional analyses

Publication bias was tested by inspecting the funnel plot on primary outcome measures and by Duval and Tweedie's (Duval & Tweedie, 2000) trim and fill procedure (as implemented in Comprehensive Meta-analysis, version 2.2.021). Duval and Tweedie's test estimates the number of missing studies that might exist in a meta-analysis due to publication bias. Trim and fill corrects for the resulting asymmetry in the funnel plot by adjusting the effect size for missing studies

(Duval & Tweedie, 2000)Egger's test of the intercept was conducted in order to quantify the bias captured by the funnel plot and test whether it was significant (M. Egger, Davey Smith, Schneider, & Minder, 1997).

Researcher allegiance for psychotherapy was examined for all the included RCTs. We evaluated a study as at high risk of researcher allegiance when any of the authors was also involved in the development of the treatment manual of the psychotherapy involved. The involvement of a researcher in developing the treatment under investigation is regarded as a valid indicator of researcher allegiance, while the validity of other indicators in reprint measures has been questioned (Munder, Brütsch, Leonhart, Gerger, & Barth, 2013).

Moderator and subgroup analyses were planned when sufficient studies (at least 3 studies per sub-group) were available.

RESULTS

After removal of duplicates, we examined 11145 references on titles and abstracts. This process resulted in 2897 articles being retrieved for possible inclusion in the present meta-analysis. In the 23 RCTs that met inclusion criteria, a total of 2184 individuals suffering from MDD participated in the relevant comparisons combined therapy, psychological and pharmacological interventions. We identified 15 RCTs on acute phase treatment and 8 RCTs on maintenance treatment. Figure 1 presents the studies selection process.

The majority of the included studies recruited their participants through clinical samples, such as general practitioners, outpatient psychiatric clinics and mental health institutes. One RCT recruited patients through both clinical and community referrals, one through community samples, and one did not report the manner of recruitment. Twenty-one of the 23 trials recruited outpatients, while two studies included inpatients. The examined RCTs were conducted across six different countries: Germany (n = 1), Italy (n = 2), China (n = 1), the Netherlands (n = 2), the United Kingdom (n = 5) and the United States (n = 12).

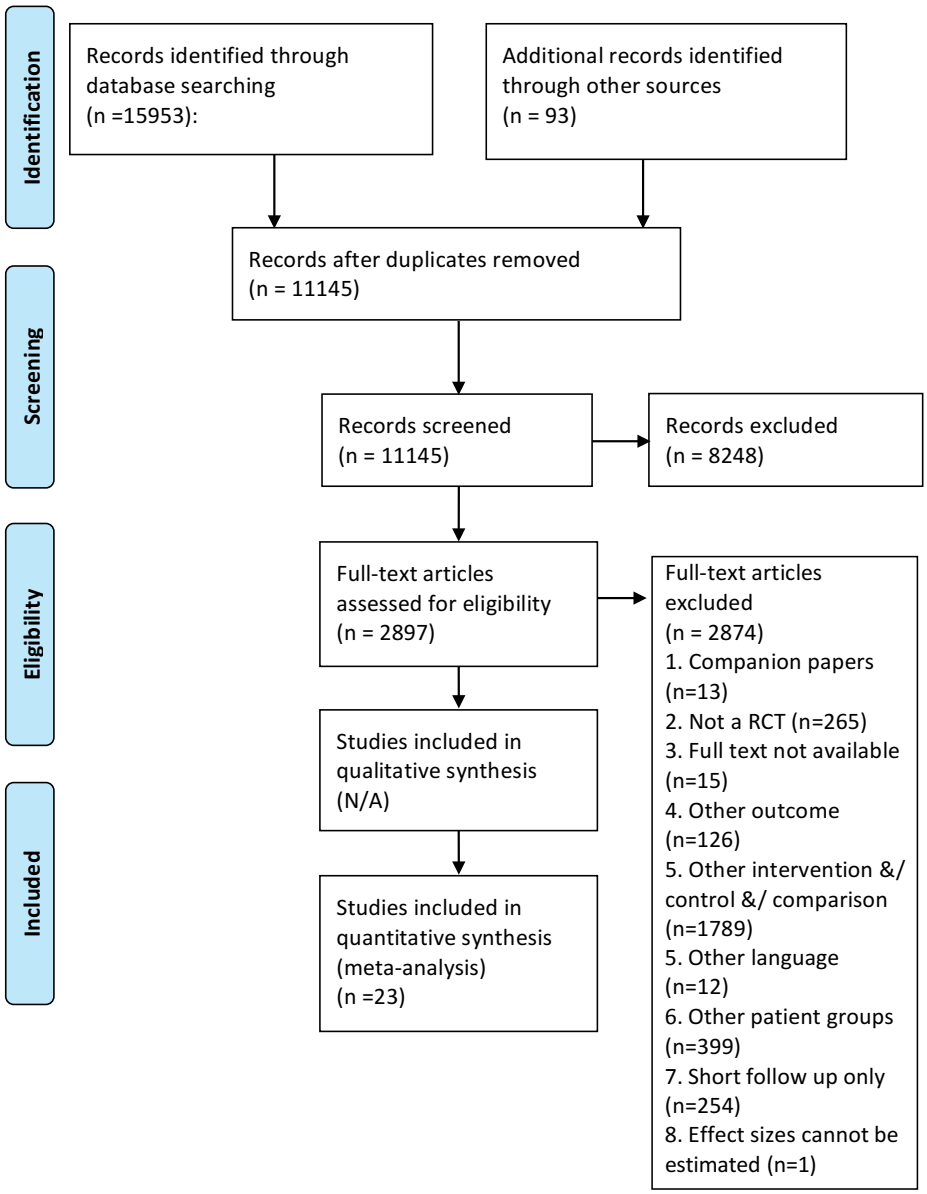

Figure 1 PRISMA flow chart of study selection process

Regarding trials on acute phase treatment, the duration of follow up ranged from six to 48 months after randomization. As for the maintenance studies, patients entered into either maintenance psychotherapy combined with antidepressants or into maintenance antidepressant medication groups and were followed from six to 24 months.

The types of psychotherapy examined across the included trials were: CBT, interpersonal psychotherapy, problem solving therapy, psychodynamic supportive therapy, and social skills training. Acute phase treatment had a duration ranging from six to 29 sessions, while the maintenance psychotherapeutic interventions consisted of six to 20 sessions that were conducted either weekly/biweekly or monthly. The antidepressant agents used were the following: amitriptyline hydrochloride, fluoxetine, fluvoxamine, imipramine hydrochloride, nortriptyline, or sertraline. Study characteristics are given in table 2.

Differences between combined psychotherapy and antidepressants vs. psychotherapy alone or antidepressants alone, acute phase treatment

Acute phase combined therapy did not differ significantly in patients' response to treatment, compared to acute phase psychotherapy at six months (OR = 1.42, 95%CI 0.97 to 2.07, $p > 0.05$) and one year or longer post randomization (OR = 1.33, 95%CI 0.88 to 2.14, $p > 0.05$). Heterogeneity between studies was zero (95% CI 0 to 71%, $p > 0.05$). There were no indications for publication bias (Table 3). However, combined psychotherapy with antidepressants (acute phase) resulted in a better treatment response compared to acute phase antidepressants after six months or longer post-randomization (OR = 2.93, 95%CI 2.15 to 3.99, $p < 0.001$). Heterogeneity between studies was zero (95%CI 0 to 57%, $p > 0.05$). There was some indication of publication bias. Duval and Tweedie's Trim and Fill procedure indicated that two studies were missing. The imputed estimate was 2.71 (95% CI 1.95 to 3.74). Nevertheless, Egger's Test was not significant ($p > 0.05$). Similar results were observed for the same comparisons after one year or longer post randomization. Combined therapy outperformed antidepressants in treatment response of outpatients with MDD (OR = 2.23, 95% CI 1.43 to 3.41). Heterogeneity was zero (95%CI 0 to 68%, $p > 0.05$). Duval and Tweedie's Trim and Fill procedure indicated a possibility for publication bias and produced an imputed estimate of 1.97 (95%CI 1.29 to 3.01), however, Egger's test was not significant (Table 4). The main outcomes are summarized in Figure 2.

Sensitivity and subgroup analyses

Two studies on inpatients were excluded in a sensitivity analysis. Acute phase combined psychotherapy with antidepressants resulted in better response to treatment compared to acute phase antidepressants at six months or longer post randomization in outpatients with MDD (OR = 2.98, 95% CI 2.07 to 4.29, $p<0.001$). Heterogeneity was low (I^2 = 8%, 95%CI 0 to 63%, $p > 0.05$). There was some indication of publication bias. Using Trim and Fill the imputed value estimate was 2.80 (95% CI 1.89 to 4.14) while Egger's test was not significant. A similar pattern of results was observed at one year or longer post randomization (Table 3). Sub-group analyses (high vs. low quality studies; CBT vs. other types of therapy; researcher allegiance vs. no researcher allegiance for psychotherapy) did not result in statistically significant differences (Table 4).

Table 2. Studies characteristics

Studies	Recruitment	Design	Any AXIS-II Diagnosis (%/ Total N)	PT	N patients	Comparison	N patients	FU (months)	Outcome	Type of treatment	RA[b]	Risk of bias[c] (0-7)	Country
Beck, Hollon, Young, Bedrosian, and Budenz (1985)	CS	RCT	9%	CBT & TCA	15	CBT	18	6, 12	BDI, HRSD	Acute	1	5	US
Bellino, Zizza, Rinaldi, and Bogetto (2006)	CS	RCT	100%	IPT & SSRI	20	SSRI	19	6	Remission (HRSD scores reduction≥40%)	Acute	0	3	IT
Blackburn, Eunson, and Bishop (1986)	CS	RCT/nat.FU	NR	CBT & TCA	16	TCA CBT	10 15	6, 12, 18, 24	Response (HRSD<8; BDI<9)	Acute	0	5	UK
de Jonghe, Kool, van Aalst, Dekker, and Peen (2001)	CS	RCT	NR	PDST & SSRI	83	SSRI	84	6	Remission (HRSD<8)	Acute	1	4	NL
de Jonghe et al. (2004); Koppers, Peen, Niekerken, Van, and Dekker (2011)	CS	RCT	NR	PDST & TCA/SSRI	101	PDST	107	6	Remission (HRSD≤7),	Acute	0	3	NL
Frank et al. (1990)	CS	RCT	NR	IPT & TCA	25	TCA	28	12, 24, 36	Recurrence (HRSD≥15); survivors (HRSD<15; Raskin<7)	Maintenance	0	4	US
Hersen, Bellack, Himmelhoch, and Thase (1984)	Com. S	RCT	NR	SS & TCA	21	TCA	14	6	Depressive symptoms (BDI; HRSD; REDS)	Maintenance	1	4	US
Evans et al.(1992); Hollon et al.(1992)	CS	RCT	NR	CBT & TCA	13	TCA CBT	10 10	24	Relapse (BDI≥16)	Acute	0	4	US

continued

Table 2. Studies characteristics (continued)

Studies	Recruitment	Design	Any AXIS-II Diagnosis (%/ Total N)	PT	N patients	Comparison	N patients	FU (months)	Outcome	Type of treatment	RA[b]	Risk of bias[c] (0-7)	Country
M. D. Evans et al. (1992); Hollon et al. (1992)	CS	RCT	NR	CBT & TCA	13	TCA CBT	10 10	24	Relapse (BDI≥16)	Acute	0	4	US
Hollon et al. (2014)	CS	RCT	49.8%	CBT &ADM (NS)	187	ADM (NS)	170	12	Recovery (>26 consecutive weeks without relapse)	Maintenance	0	1	US
Macaskill and Macaskill (1996)	CS	RCT	65%	RET & TCA	10	TCA	10	6	HRSD; BDI	Acute	0	4	UK
Maina, Rosso, and Bogetto (2009)	CS	RCT	NR	BDT & SSRI	65	SSRI	83	48	Remission (HRSD≤7)	Acute	0	4	IT
Maina, Rosso, Rigardetto, Piat, and Bogetto (2010)	Com. & CS	RCT	NR	BDT & SSRI	25	SSRI	29	12	Remission (HRSD≤7),	Acute	0	3	IT
Miller, Norman, and Keitner (1989)	Inpatients	RCT/nat.FU	NR	CBT & TCA	28	TCA	17	6, 12	Remission (HRDS≤7; BDI≤9),	Acute	0	3	US
Mynors-Wallis, Gath, Day, and Baker (2000)	CS	RCT	NR	PST & SSRI	35	SSRI PST (GP) PST (nurse)	36 39 41	13	Recovery (HRSD-17≤7)	Acute	1	1	UK
Paykel et al. (1999)	CS	RCT	NR	CBT & TCA	80	TCA	78	17	Relapse (DSM-III-R)	Maintenance	0	3	UK
Perlis et al. (2002)	NR	RCT	NR	CBT &SSRI	66	SSRI	66	6	Relapse (HRSD≥15)	Maintenance	0	4	US
Reynolds et al. (1999)	NR	RCT	NR	IPT & TCA	16	TCA	25	12	Remission (DSM-IV)	Maintenance	0	4	US

continued

Table 2. Studies characteristics (continued)

Studies	Recruitment	Design	Any AXIS-II Diagnosis (%/ Total N)	PT	N patients	Comparison	N patients	FU (months)	Outcome	Type of treatment	RA[a]	Risk of bias[b] (0-7)	Country
Reynolds Iii et al. (2006)	CS	RCT	NR	IPT & SSRI	22	SSRI	24	12	Recurrence (DSM-IV)	Maintenance	1	3	US
Schramm et al. (2007)	Inpatients	RCT/nat.FU	21%	IPT & TCA	65	TCA	65	12	Response (HRSD scores reduction ≥50%); Recovery (HRSD≤7)	Acute	0	3	DE
Simons, Murphy, Levine, and Wetzel (1986)	CS	RCT/nat.FU	NR	CBT & TCA	18	TCA CBT	16 19	12	Response (BDI<10)	Acute	0	4	US
Sirey, Bruce, and Alexopoulos (2005)	CS	RCT	NR	CBT & ADM (NS)	21	ADM (NS)	24	6	Response (HRSD≤10	Acute	1	4	US
Wilkinson et al. (2009)	CS	RCT	NR	CBT & SSRI	22	SSRI or TCA	23	6, 12	Recurrence (MADRS≥10; BDI≥12)	Maintenance	1	1	UK
Zu et al. (2014)	CS	RCT	NR	CBT SSRI	60	SSRI CBT	60 30	6	Remission QIDS<5	Acute	0	4	CH

ADM: Antidepressant Medication; BDI: Beck Depression Inventory; BDT: Brief Dynamic Therapy; CBT: Cognitive Behavioural Therapy; CH: China; CIDI: Composite International Clinical Interview; Com. S: Community Sample CS: Clinical Sample; GP: General Practitioner; DE: Germany; DSM: Diagnostic and Statistical Manual of Mental Disorders; FU: Follow Up post-randomization; GP: General Practitioner; HRSD: Hamilton Rating Scale for Depression; IPT: Interpersonal Psychotherapy; IT: Italy; M: month(s); MADRS: Montgomery Asberg Depression Rating Scale; N: number; NL: Netherlands; NR: Not Reported; NS: Not Specified; PDST: Psychodynamic Supportive Therapy; PST: Problem Solving Therapy; PT: Psychotherapy; QIDS:Quick Inventory of Depressive Symptomatology-Self- Report; RA: Research Allegiance; RCT: Randomized Controlled Trial; RCT/nat. FU: Randomized Controlled Trial/Naturalistic Follow Up; SSRI: Selective Serotonin Reuptake Inhibitor; TCA: Tricyclic antidepressant; UK: United Kingdom; US: United States; W: week(s)

[a] One (1) is given when the study was evaluated as at high risk of researcher allegiance and zero (0) when the study was evaluated as at low risk of researcher allegiance

[b] Sum of 'unclear or high risk of bias' of the individual quality criteria. The sum is derived after assigning a zero (low risk of bias) or one (unclear or high risk of bias) to each one of the following quality criteria: allocation sequence, allocation concealment, blinding of participants and personnel, blinding of assessors, incomplete outcome data, selective reporting, and other sources of bias.

Table 3. Effect sizes for combined psychotherapy and antidepressants vs. psychotherapy in adults with MDD, acute phase

Outcomes	N	OR	95% CI[b]	I^2	95%CI	p[c]
Response at 6 months or longer post randomization	8	1.42	0.97 to 2.07	0	0 to 68	
Subgroups						
Type of psychotherapy						
CBT vs.	5	1.51	0.79 to 2.86	0	0 to 79	0.50
Other	3	1.37	0.85 to 2.19	0	0 to 90	
Researcher allegiance						
No	5	1.53	0.97 to 2.40	0	0 to 79	0.60
Yes	3	1.19	0.60 to 2.40	0	0 to 90	
Response at 1 year or longer post randomization	7	1.33	0.88 to 2.14	0	0 to 71	
Subgroups						
Type of psychotherapy						
CBT vs.	4	1.48	0.59 to 3.71	0	0 to 85	0.80
Other	3	1.24	0.68 to 2.22	0	0 to 90	
Researcher allegiance						
No	4	1.36	0.82 to 2.25	0	0 to 85	0.90
Yes	3	1.28	0.64 to 2.58	0	0 to 90	

[a] Subgroup analyses were conducted only in the cases where at least three comparisons were available per group. N: Number of comparisons
[b] 95% CI: 95% Confidence Intervals; OR: Odds Ratio; p: p-value
[c] p-value betweensub- groups

Differences between combined psychotherapy with antidepressants vs. psychotherapy alone or antidepressants alone in adults who have had MDD, maintenance treatment

Only one study (Frank et al. 1990) examined the comparison between combined maintenance psychotherapy with antidepressants and maintenance psychotherapy at six months or longer post-randomization. Thus, we could not examine this comparison.

Table 5 shows the results of the comparison between maintenance combined psychotherapy and antidepressants at six months or longer post randomization. Combined maintenance psychotherapy with antidepressants resulted in a better treatment-sustained response compared to antidepressants at six months or longer post randomization (OR = 1.61, 95%CI 1.14 to 2.27, $p < 0.05$). Heterogeneity was zero (95%CI 0 to 68%, $p < 0.05$). There was no indication of publication bias. Six studies compared the outcomes of combined maintenance psychotherapy with antidepressants versus antidepressants at one year or longer post randomization. Combined maintenance psychotherapy with antidepressants resulted in a better-sustained response to treatment in comparison with antidepressants (OR = 1.73, 95% CI 1.20 to 2.49, $p < 0.05$) after one year or longer post randomization. Heterogeneity between the studies was zero (95%CI 0 to 75%, $p > 0.05$). There was no indication of publication bias. Finally, subgroup analyses (studies with high vs. studies with low risk of bias, CBT vs. other types of therapy, SSRI vs. TCA antidepressants, and researcher allegiance vs. no researcher allegiance for psychotherapy) did not result in statistically significant differences.

The main outcomes of our analyses are summarized in Figure 2. The forest plots of the main outcomes can be found in Appendix C.

Table 4. Effect sizes for combined psychotherapy with antidepressants vs. antidepressants in adults with MDD, acute phase

Outcomes	N	OR	95% CI[b]	I^2	95%CI	p[c]
Response at 6 months or longer post randomization	13	2.93*	2.15 to 3.99	0	0 to 57	
Subgroups						
Type of psychotherapy						
CBT vs.	6	3.02*	1.74 to 5.25	0	0 to 75	0.88
Other	7	2.87*	1.77 to 4.64	32	0 to 71	
Risk of bias						
Risk of bias ≤ 3vs.	4	1.66	0.98 to 2.81	0	0 to 85	0.17
Risk of bias > 3	5	2.26*	1.35 to 3.78	13	0 to 82	
Types of antidepressants						
SSRI	6	2.64*	1.70 to 4.11	19	0 to 64	0.51
TCA	6	3.37*	1.90 to 5.99	0	0 to 75	
Response at 1 year or longer post randomization	8	2.23*	1.43 to 3.41	0	0 to 68	
Subgroups						
Type of psychotherapy						
CBT vs.	4	3.37*	1.38 to 8.21	0	0 to 85	0.29
Other	4	1.94*	1.16 to 3.23	0	0 to 85	
Risk of bias						
Risk of bias ≤ 3 vs.	4	1.94*	1.16 to 3.23	0	0 to 85	0.29
Risk of bias > 3	4	3.37*	1.38 to 8.21	0	0 to 85	
Types of antidepressants						
SSRI	3	1.64	0.84 to 3.18	0	0 to 90	0.22
TCA	5	2.84	1.57 to 5.16	0	0 to 79	
Sensitivity analysis						
Response at 6 months or longer post randomization (inpatients excluded)	11	2.98*	2.07 to 4.29	8	0 to 63	
Response at 1 year or longer post randomization (inpatients excluded)	6	1.99*	1.14 to 3.47	0	0 to 75	

[a] Subgroup analyses were conducted only in the cases where at least three comparisons were available per group. N: Number of comparisons
[b] 95% CI: 95% Confidence Intervals; OR: Odds Ratio; p: p-value
[c] p-value between sub-groups
** p < 0.05*

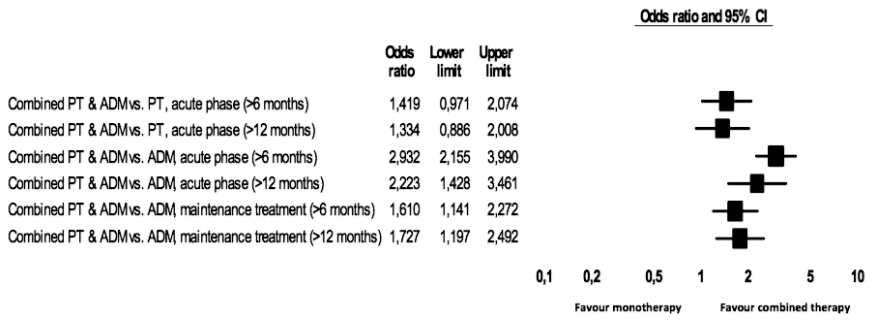

Figure 2. Main outcomes of combined psychotherapy and antidepressant medications (PT&ADM) in Odds ratio (OR) and 95% confidence intervals

Table 5. Effect sizes maintenance psychotherapy with antidepressants vs. antidepressants in adults with MDD

Outcomes	N	OR	95% CI[b]	I^2	95%CI	p[c]
Sustained response at 6 months or longer post randomization	8	1.61*	1.14 to 2.27	0	0 to 68	
Subgroups						
Type of psychotherapy						
CBT vs.	4	1.79*	1.19 to 2.70	0	0 to 85	0.32
Other	4	1.23	0.64 to 2.33	0	0 to 85	
Risk of bias						
Risk of bias ≤ 3	5	1.75*	1.20 to 2.56	0	0 to 79	0.28
Risk of bias > 3	3	1.07	0.47 to 2.45	0	0 to 90	
Researcher allegiance						
No	5	1.80*	1.21 to 2.65	0	0 to 79	0.26
Yes	3	1.12	0.55 to 2.30	0	0 to 90	
Types of antidepressants						
SSRI	3	1.26	0.60 to 2.64	0	0 to 90	0.43
TCA	4	1.81*	1.08 to 3.03	0	0 to 85	
Sustained response at 1 year or longer post randomization	6	1.73*	1.20 to 2.49	0	0 to 75	

[a] Subgroup analyses were conducted only in the cases where at least three comparisons were available per group. N: Number of comparisons
[b] 95% CI: 95% Confidence Intervals; OR: Odds Ratio; p: p-value
[c] p-value between groups
** p < 0.05*

DISCUSSION

The aim of the present meta-analysis was to examine to what extent combined pharmacotherapy with psychotherapy results in a different long-term response to treatment compared to psychotherapy and pharmacotherapy alone in adults with major depression. Results indicated that combined psychotherapy with antidepressants resulted in an equal acute phase treatment response compared to psychotherapy at six months or longer post randomization, in adult patients with MDD. Further, combined psychotherapy with antidepressants resulted in a better acute phase treatment response compared to antidepressants alone, at six months or longer post-randomization. As for the maintenance studies, there was evidence that maintenance-combined psychotherapy with antidepressants resulted in a better-sustained response compared to maintenance antidepressants alone, at six months or longer post-randomization.

The results of the comparison between combined therapies versus antidepressants alone (acute phase treatment) may have been somewhat overestimated due to publication bias. This indication of publication bias is in accordance with previous meta-analyses on the same comparison (Cuijpers et al., 2014). However, the point estimate remained high and significant after the adjustment for publication bias.

The results of the present meta-analysis are in line with previous research, which compared the effects of combined therapy against antidepressants in patients with depression and anxiety disorders in the short term (Cuijpers & Dekker, 2005; Cuijpers, Dekker, et al., 2009; Cuijpers,

Reynolds, et al., 2012; Cuijpers et al., 2014; Khan et al., 2012; Pampallona et al., 2004). A recent meta-analysis by P. Cuijpers et al. (2014) showed that adding psychotherapy to antidepressants results in overall superior short-term effects compared to antidepressants alone in patients with MDD, panic disorder and obsessive compulsive disorder. The authors also reported that these effects were sustained during 2 years follow-up (Cuijpers et al., 2014). The present findings are also in line with the results of Barber et al. (2013) on dynamic therapy. The authors found that in the long-term dynamic therapy combined with antidepressants results in higher remission rates compared to antidepressants alone in adults with depression (Barber et al., 2013). Moreover, the finding that acute phase combined therapy results in no differences in treatment response compared to acute psychotherapy in longer than 6 months post-randomization is in accordance with Cuijpers, van Straten, et al. (2009) meta-analysis. Cuijpers, van Straten, et al. (2009) showed that there are no differences between the effects of combined therapy and psychotherapy at longer than 1 month follow up in patients with depression (Cuijpers, A. van Straten, et al., 2009). To the best of our knowledge there is no systematic review examining the effects of maintenance combined therapy.

The present study has several strengths. The included studies targeted outpatients with MDD and thus, the results of the present review refer to a highly homogeneous population. Additionally, our results are based on a direct comparison between acute/maintenance phase combined treatment and acute phase antidepressants/psychotherapy or maintenance antidepressants.

However, the present results should be interpreted with caution due to several limitations. Most of the included trials used CBT as a psychotherapeutic intervention, therefore, differences between different types of psychotherapy could not be examined and the generalizability of the present findings to all types of psychotherapy is restricted. Similarly, a distinction between depression severities was not possible because there were no specific studies with a distinction between mild, moderate and severe MDD. The outcome was specified to treatment response since the included studies did not provide enough information on outcomes assessed by clinical interview. Furthermore, we identified only one trial on the comparison between maintenance combined therapy and psychotherapy alone (Frank et al., 1990). Thus, we could not analyze this comparison and we limited our analysis to the comparison between maintenance-combined therapy against maintenance antidepressants. Finally, a limitation that should be acknowledged is that the sample at randomization is typically not the same as the one at long-term follow-up, in spite of using advanced statistics to model missing data.

With respect to researcher allegiance, a bias of concern in psychotherapy research (Munder et al., 2013), we did not find evidence that studies at a high risk of researcher allegiance for psychotherapy favored psychotherapy more than did studies at a low risk of researcher bias. However, the number of studies in each subgroup was small, and we did not examine more subtle forms of researcher allegiance for psychotherapy such as whether authors advocated the psychotherapy or the mix of research teams (including methodologists and/or psychiatrists).

As for our own researcher allegiance, we have carried out in the past a series of meta-analyses of several different types of psychotherapy and pharmacotherapy and we do not prefer one treatment to another. Additionally, we believe that out team is well balanced as it consists of researchers in clinical psychology as well as experts in evidence-based medicine.

The results of this meta-analysis raise several clinical possibilities. Currently, antidepressants are widely used as first option in treating major depression in primary and secondary mental health care (Geddes et al., 2003). Given the high risk of relapse (Keller, 1994), alternative treatment options should also be proposed. The present findings highlight that the combination of psychotherapy with antidepressants provides clinical gains in terms of long-term sustainability of the treatment response. Thus, in light of the enduring effects, combined therapy may be preferred over monotherapy with antidepressants in treatment of major depression.

However, while combined therapy enhanced response rates relative to antidepressant alone, the present results failed to demonstrate a superiority of combined treatment compared to psychotherapy alone, after acute phase treatment. This might be due to the limited number of trials on the comparison between combined therapy and psychotherapy alone and it remains to be confirmed by future studies. However, it could also indicate that psychotherapy is in fact a viable alternative for combined treatment, which is important to note for several reasons. Psychotherapy in contrast to medication is not related to side effects (National Collaborating Centre for Mental Health, 2010a) and teaches patients a set of skills and coping mechanisms, which they can employ and use to sustain their improvement after the treatment phase is over. Furthermore, in evidence based practice the decision-making is based on both treatment effectiveness and patient preferences. Considering that combined therapy and psychotherapy alone result in equivalent outcomes over the long-term, patients' preferences is an important factor when choosing treatment modality. Previous research has shown that some patients prefer psychotherapy to taking medication (van Schaik et al., 2004); thus, access to both psychotherapy and pharmacotherapy in primary and secondary mental health care may increase the chance of patients following their preferred treatment (Winter & Barber, 2013).

Further research is warranted to address outcomes such as quality of life or adverse events, and to examine more types of psychotherapy. To conclude, the present results suggest that combined treatment is the best available option both as acute and as maintenance therapy for treating major depression in the long term. In addition, if a patient does not prefer the combined treatment, acute phase psychotherapy could also be a treatment option as it is as effective as acute phase combined treatment in the long term.

CHAPTER 4

PSYCHOLOGICAL TREATMENT OF DEPRESSION IN LOW AND MIDDLE-INCOME COUNTRIES: A META-ANALYSIS

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World Psychiatry

ABSTRACT

Most psychological treatments for depression have been developed in the high-income, Western countries in North America, Europe and Australia. A growing number of randomized trials have examined the effects of these treatments in non-Western countries. We conducted a meta-analysis of these studies to examine whether these psychotherapies are effective and to compare the effects between studies from Western and non-Western countries. We conducted systematic searches in bibliographical databases and included 253 randomized controlled trials, of which 32 were conducted in non-Western countries. The effects of psychotherapies in non-Western countries were large (g=1.10; 95% CI: 0.91 to 1.30), with high heterogeneity (I^2=90; 95% CI: 87 to 92). After adjustment for publication bias the effect size dropped to g=0.73 (95% CI: 0.51 to 0.96). Subgroup analyses did not indicate that adaptation to the local situation was associated with the effect size. Comparisons with the studies in Western countries showed that the effects of the therapies are significantly larger in non-Western countries, also after adjusting for characteristics of the participants, the treatments and the studies. These larger effect sizes in non-Western countries may reflect true differences indicating that therapies are indeed more effective, or they may be explained by the care-as-usual control conditions that in non-Western countries often indicate that no care was available, or this may be the result of the relative low quality of many trials in this field. This study suggests that psychological treatments that were developed in Western countries may or may not be more effective in non-Western countries, but they are probably no less effective and can therefore also be used in non-Western countries, regardless of the income level of that country.

INTRODUCTION

Depression and other common mental disorders are highly prevalent with almost one in five people worldwide affected (Kessler et al., 2005; Steel et al., 2014). They have a considerable impact on the lives of patients and their families, and are associated with huge economic and societal costs (Smit et al., 2007). The disability associated with these disorders results in a loss of more than one million healthy life years, which makes mental disorders the leading cause of years lived with disability worldwide (Whiteford et al., 2013). The economic costs, in terms of production losses and in health and social care expenditures have been estimated at US$ 2.5 trillion in 2010 worldwide (Chisholm et al., 2016; Gustavsson et al., 2011; Hu, 2006), and these costs are expected to grow to US$ 6.0 trillion by 2030 (Bloom et al., 2012).

Several evidence-based pharmacological and psychological treatments are available for depression. However, most people with a depressive disorder do not receive treatment, especially in low and middle-income countries, where between 7 and 21% of patients are treated (Chisholm et al., 2016). And if patients get treatment this typically consists of pharmacotherapy, while the majority of patients prefer psychological treatment (McHugh et al., 2013).

Several psychological interventions such as cognitive behavior therapy, interpersonal psychotherapy, problem-solving and behavioral activation have been developed for the treatment of depression (Cuijpers, 2014). Since the 1970s several hundreds of randomized trials have examined the effects of these interventions and have shown they are effective (Cuijpers, Matthias Berking, et al., 2013a; Cuijpers, Geraedts, et al., 2011; Cuijpers et al., 2007b; David Ekers et al., 2014), although these effects are modest and have been overestimated because of the low quality of many trials (Cuijpers, van Straten, Bohlmeijer, Hollon, & Andersson, 2010a) and publication bias (Cuijpers, Smit, Bohlmeijer, Hollon, & Andersson, 2010; Driessen et al., 2015). The effects of psychotherapies have been found to be comparable to those of pharmacotherapy (Cuijpers et al., 2013) and probably last longer than those of pharmacotherapy (Karyotaki et al., 2016).

However, most psychological treatments have been developed in the high-income, Western countries in North America, Europe and Australia. And although more than 450 randomized trials have examined the effects of psychotherapies (Cuijpers, Annemieke van Straten, et al., 2008a), by far the majority of these trials have been conducted in high-income Western countries. It is therefore not well known whether these therapies are also effective in low and middle-income countries.

In recent years a growing number of randomized trials have examined the effects of psychological treatments in depression in non-Western countries outside of North America, Europe and Australia. The goal of the current meta-analysis is to examine whether these psychotherapies are also effective in non-Western countries and to compare the effects with those from Western

countries. This also gives the opportunity to examine whether the effects of psychotherapies are associated with the income of the country and the region where the trial was conducted.

METHODS

Identification and selection of studies

We used an existing database of studies on the psychological treatment of depression. This database has been described in detail elsewhere (Cuijpers, Annemieke van Straten, et al., 2008a), and has been used in a series of earlier published meta-analyses (Cuijpers, Andersson, et al., 2011). For this database we searched four major bibliographical databases (PubMed, PsycInfo, Embase and the Cochrane Library) by combining terms (both index terms and text words) indicative of depression and psychotherapies, with filters for randomized controlled trials. The full search string for one database (PubMed) is given in Appendix A. We also checked the references of earlier meta-analyses on psychological treatments for the included disorders. The database is continuously updated and was developed through a comprehensive literature search (from 1966 to January, 1st 2016). All records were screened by two independent researchers and all papers that could possibly meet inclusion criteria according to one of the researchers were retrieved as full-text. The decision to include or exclude a study in the database was also done by the two independent researchers, and disagreements were solved through discussion.

Because this database was not developed specifically for including studies from non-Western countries, we searched a selection of databases from the list that has been made by the Effective Practice and Organisation of Care (EPOC) Group (a Cochrane Review Group). This list contains a collection of databases, web sites and journals relevant to Low- and Middle-Income Countries (LMICs). We selected bibliographical database that were freely available, could be searched in English, and had a working web-address. We searched the following databases with adapted search strings: 3ie (International Initiative for Impact Evaluation); British Library for Development Studies; Eldis; WHO Global Index Medicus; LILACS; IBECS; AfricaBib database on African women; IndMed; Korea med; and African Journals online; date of the search: November 2016).

Depression could be established with a diagnostic interview or with a score above a cut-off on a self-report measure. Psychotherapeutic interventions were defined as interventions with a primary focus on language-based communication between a patient and a therapist, or as bibliotherapy supported by a therapist (Barth et al., 2013). The therapies could be delivered individually, in groups, or as guided self-help by professionals or paraprofessionals. Co-morbid mental or somatic disorders were not used as an exclusion criterion. Studies on inpatients were excluded. We also excluded maintenance studies, aimed at people who had already recovered or partly recovered after an earlier treatment.

In addition to the main analyses of the studies conducted in non-Western countries, we also compared treatment effect sizes in the trials conducted in non-Western countries with those

conducted in Western countries. For this comparison we selected trials from our database of trials on psychotherapies for depression that were conducted in Western countries and in which psychotherapy was compared with a control condition, with the same in- and exclusion criteria as for the studies in non-Western countries.

Quality assessment and data extraction

We assessed the validity of included studies using four criteria of the 'Risk of bias' assessment tool, developed by the Cochrane Collaboration (JPT Higgins et al., 2011). This tool assesses possible sources of bias in randomized trials, including the adequate generation of allocation sequence; the concealment of allocation to conditions; the prevention of knowledge of the allocated intervention (masking of assessors); and dealing with incomplete outcome data (this was assessed as positive when intention-to-treat analyses were conducted, meaning that all randomized patients were included in the analyses). Assessment of the validity of the included studies was conducted by two independent researchers, and disagreements were solved through discussion.

We also coded participant characteristics (depressive disorder of scoring high on a self-rating scale; recruitment method; target group); characteristics of the psychotherapies (treatment format; number of sessions); and general characteristics of the studies (type of control group; country where the study was conducted).

We rated whether the intervention was adapted to the local setting and population. We considered an intervention not adapted when the authors did not mention adaptation and when the procedures described were comparable to those found in therapies developed in Western countries. An intervention was considered as adapted when it was explicitly mentioned that the intervention was adapted to the local situation. We considered an intervention also as "adapted" when it was developed in a non-Western country, and was based on models or theories from non-Western countries. We also considered an intervention as 'not sufficiently adapted' when western manuals were only translated into the national language.

In order to examine whether the effects of psychotherapy are associated with the per capita income, we collected the Gross National Income (GNI) based on Purchasing Power Parity (PPP) per capita in international Dollars for each of the countries where a trial was conducted, using data from the World bank (http://data.worldbank.org/indicator/NY.GNP.PCAP.CD). We categorized the countries into low-, lower-middle, upper-middle and high-income countries according to the definition of the World bank (http://data.worldbank.org/about/country-and-lending-groups). We also used the seven World Bank regions to categorize where the studies were conducted (East Asia and Pacific, Europe and Central Asia, Latin America and the Caribbean, Middle East and North Africa, South Asia and Sub-Saharan Africa, and high-income countries).

Primary outcome

For each comparison between a psychotherapy and a control condition, the effect size indicating the difference between the two groups at post-test was calculated (Hedges' g). Effect sizes of 0.8 can be assumed to be large, while effect sizes of 0.5 are moderate, and effect sizes of 0.2 are small (Cohen, 1988). Effect sizes were calculated by subtracting (at post-test) the average score of the psychotherapy group from the average score of the control group, and dividing the result by the pooled standard deviation. Because some studies had relatively small sample sizes we corrected the effect size for small sample bias (Hedges & Olkin, 1985). If means and standard deviations were not reported, we used the procedures of the Comprehensive Meta-Analysis software (see below) to calculate the effect size using dichotomous outcomes; and if these were not available either, we used other statistics (such a *t*-value or *p*-value) to calculate the effect size.

In order to calculate effect sizes we used all measures examining depressive symptoms [such as the Beck Depression Inventory/BDI; Beck, Ward, and Mendelson (1961), the BDI-II; Beck, Steer, and Brown (1996); or the Hamilton Rating Scale for Depression/HAMD-17, Hamilton (1960)].

Meta-analyses

To calculate pooled mean effect sizes, we used the computer program Comprehensive Meta-Analysis (version 3.3070; CMA). Because we expected considerable heterogeneity among the studies, we employed a random effects pooling model in all analyses.

Numbers-needed-to-be-treated (NNT) were calculated using the formulae provided by Furukawa (Furukawa, 1999) , in which the control group's event rate was set at a conservative 19% (based on the pooled response rate of 50% reduction of symptoms across trials in psychotherapy for depression) (Cuijpers et al., 2014). As a test of homogeneity of effect sizes, we calculated the I^2-statistic, which is an indicator of heterogeneity in percentages. A value of 0% indicates no observed heterogeneity, and larger values indicate increasing heterogeneity, with 25% as low, 50% as moderate, and 75% as high heterogeneity (Higgins, Thompson, Deeks, & Altman, 2003). We calculated 95% confidence intervals around I^2 (Ioannidis, Patsopoulos, & Evangelou, 2007) using the non-central chi-squared-based approach within the heterogi module for Stata (Orsini et al., 2006). We conducted sensitivity analyses excluding potential outliers. These were defined as studies of which the 95% CI of the effect size did not overlap with the 95% CI of the pooled effect size.

We conducted subgroup analyses according to the mixed effects model, in which studies within subgroups are pooled with the random effects model, while tests for significant differences between subgroups are conducted with the fixed effects model. For continuous variables, we used meta-regression analyses to test whether there was a significant relationship between the continuous variable and effect size, as indicated by a Z-value and an associated p-value. Multivariate meta-regression analyses, with the effect size as the dependent variable, were conducted in CMA.

We tested for publication bias by inspecting the funnel plot on primary outcome measures and by Duval and Tweedie's trim and fill procedure (Duval & Tweedie, 2000), which yields an estimate of the effect size after the publication bias has been taken into account (as implemented in CMA). We also conducted Egger's test of the intercept to quantify the bias captured by the funnel plot and to test whether it was significant.

RESULTS

Selection and inclusion of studies

After examining a total of 16,908 abstracts (13,774 after removal of duplicates), we retrieved 1,888 full-text papers for further consideration. We excluded 1,635 of the retrieved papers. The PRISMA flowchart describing the inclusion process, including the reasons for exclusion, is presented in Figure 1. A total of 32 studies conducted in non-Western countries (with 35 comparisons between a psychotherapy and a control condition; four studies compared two types of psychotherapy with the same control condition) met inclusion criteria for this meta-analysis (Table 1).

Another 221 studies (with 297 comparisons between a treatment and a control group) on psychological treatments in Western countries were included (for the comparison of effect sizes of psychological treatments in Western versus non-Western countries). This makes a total of 253 studies that were included in the analyses.

Characteristics of included studies

Selected characteristics of the included Non-Western studies are presented in Table 1. In the 32 included studies conducted in Non-Western countries, a total of 4607 patients participated (therapy conditions = 2222, control conditions = 2385). Participants were recruited through: (a) announcements in local newspapers and other media (four studies), (b) referrals from health services (11 studies), and (c) other recruitment strategies (such as screening at general medical services; 17 studies).

In 25 of the 35 comparisons between a treatment and a control condition, cognitive behavior therapy was used as the intervention, two used interpersonal psychotherapy, one used psychodynamic therapy, one used non-directive supportive therapy and the remaining six used another type of treatment. Of these treatments, 10 were culturally adapted, 22 were not culturally adapted, and three were Non-Western treatments.

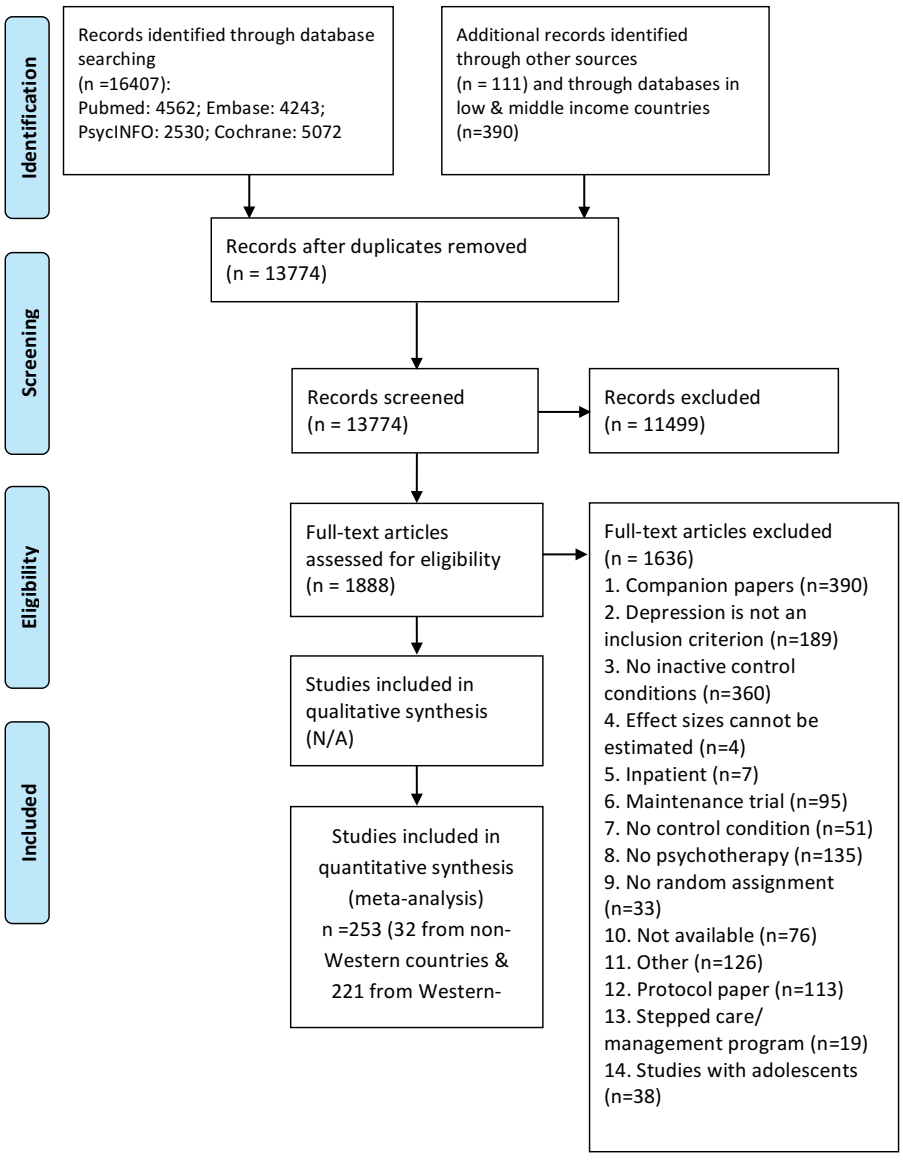

Figure 1. PRISMA flow chart of study selection process

Table 1. Selected characteristics of randomized trials comparing psychotherapies for adult depression to control groups in non-Western countries

Study	*Target Group*	*Diagn*	*Recr*	*Conditions*	N_{cond}	*For-mat*	*Cult Ad*	N_{sess}	*Coun-try*	*Income* [a]	*GNI*	*RoB* [b]
Bolton et al. (2003)	Adults	Mood Disorder	Other	IPT CAU	139 145	Grp	Cult Ad	16	Uganda	L/L-M	250	+ – SR +
Chan et al. (2012)	Adults	MDD	Clin	CBT MBT WL	17 17 16	Ind	Not Ad Non-Wes	10 10	China	U-M	5.870	– + + –
Chan et al.(2013)	Older Adults	Other	Other	Other CAU	14 12	Ind	Non-Wes	5	China	U-M	6.710	+ – SR +
Chen, Tseng, Chou, and Wang (2000)	Women with PPD	Other	Other	SUP CAU	30 30	Grp	Not Ad	4	Taiwan	High	14000	– – SR –
Chiang et al. (2015)	Adults	Mood Disorder	Clin	CBT CAU	30 32	Grp	Not Ad	12	Taiwan	High	47.830	+ + + –
Cho, Kwon, and Lee (2008)	Women with PPD	Mood Disorder	Other	CBT CAU	12 10	Ind	Not Ad	9	Korea	L/L-M	22.850	– – SR –
Duarte, Miyazaki, Blay, and Sesso (2009b),	General Med. Dis.	MDD	Other	CBT CAU	41 44	Grp	Not Ad	12	Brasil	U-M	7.990	– + SR –
Faramarzi et al. (2008)	Other	MDD	Other	CBT CAU	29 30	Grp	Not Ad	10	Iran	U-M	4.820	– – SR –
T. A. Furukawa et al. (2012)	Adults	Subthres-hold	Other	CBT WL	58 60	Ind	Cult Ad	8	Japan	High	47.830	+ + SR +
García-Peña et al. (2015)	Older Adults	Other	Clin	CBT CAU	41 40	Grp	Not Ad	12	Mexico	U-M	9.870	+ – SR –
Hamdan-Mansour, Puskar, and Bandak (2009)	Students	Other	Comm	CBT CAU	44 36	Grp	Cult Ad	10	Jordan	U-M	3.900	– + SR –
Hou et al. (2014)	Women with PPD	Mood Disorder	Other	CBT CAU	104 109	Other	Not Ad	19	China	U-M	7.400	– – SR –
Huang et al. (2015)	General Med. Dis.	Other	Other	CBT CAU	31 30	Grp	Not Ad	12	Taiwan	High	47.830	– – SR –

continued

Table 1. Selected characteristics of randomized trials comparing psychotherapies for adult depression to control groups in non-Western countries (continued)

Study	*Target Group*	*Diagn*	*Recr*	*Conditions*	N_{cond}	*For-mat*	*Cult Ad*	N_{sess}	*Coun-try*	*Income* [a]	*GNI*	*RoB* [b]
Jiang et al. (2014)	Women with PPD	Other	Other	Other CAU	257 514	Ind	Not Ad		China	U-M	7.400	+ – SR –
Leung et al. (2013)	Women with PPD	Other	Other	CBT CAU	47 50	Grp	Cult Ad	6	China	U-M	6.710	– – SR +
Liu et al. (2009)	Adults	Other	Comm	CBT WL	27 25	Gsh	Not Ad	10	Taiwan	High	47.830	– – SR –
Mukhtar (2011)	Adults	Mood Disorder	Other	CBT WL	58 55	Grp	Cult Ad	8	Malaysia	U-M	9.080	– – SR –
Naeem et al. (2014)	Adults	Mood Disorder	Clin	CBT CAU	94 89	Gsh	Cult Ad	7	Pakistan	L/L-M	1.400	+ – SR –
Nakimuli-Mpungu et al. (2015)	General Med. Dis.	Mood Disorder	Other	SUP Other	57 52	Grp	Cult Ad	8	Uganda	L/L-M	670	+ + SR +
Ng, Tien, Thayala, Ho, and Chan (2013)	Older Adults	Other	Other	Other CAU	14 12	Ind	Not Ad	5	Singapore	High	54.580	– – SR –
Ngai, Wong, Leung, Chau, and Chung (2015)	Women with PPD	Other	Other	CBT CAU	197 200	Other	Cult Ad	5	China	U-M	7.400	+ + SR +
Omidi, Mohammadkhani, Mohammadi, and Zargar (2013)	Adults	MDD	Clin	CBT MBCT CAU	30 30 30	Grp Grp	Not Ad Not Ad	8 8	Iran	U-M	7.120	– – SR –
Petersen, Hanass Hancock, Bhana, and Govender (2014)	General Med. Dis.	MDD	Other	IPT CAU	17 17	Grp	Cult Ad	8	South Africa	U-M	6.800	+ – SR –
Qiu, Chen, Gao, Xu, Tong, Yang, et al. (2013)	General Med. Dis.	MDD	Other	CBT WL	31 31	Grp	Not Ad	10	China	U-M	6.710	+ + + +

continued

Table 1. Selected characteristics of randomized trials comparing psychotherapies for adult depression to control groups in non-Western countries (continued)

Study	*Target Group*	*Diagn*	*Recr*	*Conditions*	N_{cond}	*For-mat*	*Cult Ad*	N_{sess}	*Coun-try*	*Income* [a]	*GNI*	*RoB* [b]
Rahman, Malik, Sikander, Roberts, and Creed (2008)	Women with PPD	MDD	Other	CBT Other	418 400	Ind	Cult Ad	16	Pakistan	L/L-M	1.020	+ + + –
Songprakun and McCann (2012)	Adults	MDD	Clin	CBT CAU	26 28	Gsh	Not Ad	8	Thailand	U-M	5.610	+ + + –
Sreevani et al. (2013)	Adults	Mood Disorder	Clin	Other CAU	15 15	Grp	Non-Wes	4	India	L/L-M	1.530	+ – SR –
Teichman, Bar-el, Shor, Sirota, and Elizur (1995)	Adults	Mood Disorder	Clin	CMT CBT WL	15 115	Ind Ind	Not Ad Not Ad	13 13	Israel	High	14.210	– – SR –
Vitriol, Ballesteros, Florenzano, Weil, and Benadof (2009)	Other	Mood Disorder	Clin	DYN CAU	44 43	Ind	Not Ad	12	Chile	High	10.030	– – + +
Wong (2008a)	Adults	MDD	Comm	CBT WL	48 40	Grp	Cult Ad	10	China	U-M	3.070	– + SR +
Wong (2008b)	Adults	MDD	Comm	CBT WL	163 159	Grp	Cult Ad	10	China	U-M	3.070	– + SR –
Si Zu et al. (2014)	Adults	MDD	Clin	CBT CAU	12 16	Ind	Not Ad	20	China	U-M	7.400	+ – + –

Note. CAU = Care as Usual; CBT = Cognitive Behavioral Therapy; Clin = participants recruited in a clinical setting; CMT: Cognitive Marital Therapy; Comm = participants recruited in a community setting; CT: Cognitive Therapy; Cult Ad: Cultural Adaptation; Diagn: Diagnosis; DR: Psychodrama; DYN: Psychodynamic Therapy; GNI: Gross National Income in US$; Grp = group format; Gsh = guided self-help format; Ind = individual format; IPT: Interpersonal Psychotherapy; L/L-M: Low/lower middle; MBCT: Mindfulness Based Cognitive Therapy; MDD = Major Depressive Disorder; Med. Dis.: Medical Disorder; Non-Wes: Non-Western Therapy; Ncond: Number of participants per condition; Nsess: Number of sessions; Not Ad: Not Culturally Adapted; Nsess: Number of sessions; PPD; Post-Partum Depression; Recr: Recruitment; RoB: Risk of Bias; SUP: Nondirective Supportive Therapy; U-M: Upper middle; WL: Waitlist.

[a] Countries in this column were categorized into low-, lower-middle-, upper-middle- and high-income countries according to the definition of the Worldbank, which can be accessed at: http://data.worldbank.org/about/country-and-lending-groups

[b] In this column a positive (+) or negative (–) sign is given for four quality criteria of the study, respectively: allocation sequence; concealment of allocation to conditions; blinding of assessors; and intention-to-treat analyses. Sr in the third criterion indicates that only self-report measures (and no assessor) were used.

Eighteen comparisons used a group treatment format, 12 studies utilized individual treatment and three used a guided self-help treatment format. The number of treatment sessions ranged from four to 20. For the control group, eight studies used a waiting list, 22 studies used care-as-usual, and two used another control group. Nineteen studies were conducted in East Asia, three were conducted in South Asia, three were conducted in Latin America and the Caribbean, four were conducted in the Middle East and North Africa, and three were conducted in Africa. The gross national income of the countries ranged from low/low-medium (250 US dollars) to high (54.580 US dollars).

Selected characteristics of the 221 Western studies (with 295 comparisons between treatment and control groups) are presented in Appendix D1 and the references for these studies are given in Appendix D2.

Effects of psychotherapies in non-Western countries

The overall effect in the 35 comparisons between therapy and control groups was g=1.10 (95% CI: 0.91 to 1.30), which corresponds with a NNT of 2.51. Heterogeneity was very high (I^2=90; 95% CI: 87 to 92). Effect sizes and 95% confidence intervals of each study are presented in the forest plot in Figure 2. The results of these main analyses are presented in Table 2.

When we limited the outcomes measured with the HAM-D-17 the mean effect size was g=1.38 (95% CI: 0.66 to 2.09; N comparisons: 7; NNT=1.99; I^2=93; 95% CI: 89 to 95). When we limited the outcomes measured with the BDI-I it was g=1.33 (95% CI: 0.54 to 2.12; N comparisons: 9; NNT=2.06; I^2=93; 95% CI: 90 to 95), and limited to the BDI-II it was g=1.37 (95% CI: 0.76 to 1.97; N comparisons: 7; NNT=2.01; I^2=91; 95% CI: 85 to 94).

Six studies were potential outliers. After exclusion of these outliers the effects dropped to g=0.95 (95% CI: 0.82 to 1.08; NNT=2.95). Heterogeneity was still moderate (I^2=55; 95% CI: 23 to 70). There were three potential outliers with extremely high effect sizes (g>2.0). The pooled effect size after excluding these extreme outliers was g=0.87 (95% CI: 0.73 to 1.06; I^2=78; 95% CI: 69 to 83).

In this meta-analysis, we included three studies in which two psychological treatments were compared with the same control group. This means that multiple comparisons from these studies were included in the same analysis. These comparisons are not independent of each other and this may have resulted in an artificial reduction of heterogeneity and may have affected the pooled effect size. We examined the possible effects of this by conducting an analysis in which we included only one effect size per study. First, we included only the comparisons with the largest effect size from these studies and then we conducted another analysis in which we included only the smallest effect sizes. As can be seen from Table 2, the resulting effect sizes were almost the same as in the overall analyses. Heterogeneity was still very high in these analyses.

Table 2. Psychotherapies for adult depression in non-Western countries compared with control conditions: Hedges' g

		*N*comp	*g*	95% CI	I^2	95% CI	*p*	NNT
All studies		35	1.10	0.91~1.30	90	87~92		2.51
One effect size per study (highest only)		32	1.11	0.90~1.32	90	88~92		2.49
One effect size per study (lowest only)		32	1.06	0.85~1.27	90	88~92		2.62
Outliers excluded [a)]		26	0.95	0.82~1.08	55	23~70		2.95
Extreme positive outliers excluded [b)]		32	0.87	0.73~1.06	78	69~83		3.26
Only HAM-D		7	1.38	0.66~2.09	93	89~95		1.99
Only BDI-I		9	1.33	0.54~2.12	93	90~95		2.06
Only BDI-II		7	1.37	0.76~1.97	91	85~94		2.01
Adjusted for publication bias (9 imputed)		44	0.73	0.51~0.96	93	92~94		3.98
Subgroup analyses								
Region	East Asia	17	0.83	0.64~1.02	77	61~84	0.55	3.44
	Middle East	6	1.17	0.69~1.65	74	18~87		2.35
	South Asia	3	0.86	0.47~1.25	77	0~91		3.30
	Other	6	0.73	0.30~1.16	85	64~91		3.98
Income country	High	8	0.86	0.48~1.23	71	24~84	0.95	3.30
	Upper middle	18	0.89	0.71~1.08	77	63~84		3.18
	Low/lower middle	6	0.83	0.44~1.22	88	76~93		3.44
Risk of Bias	0-1 (high)	10	1.20	0.84~1.56	73	42~84	<0.001	2.29
	2-3	16	0.87	0.70~1.03	61	22~76		3.26
	4 (low)	6	0.51	0.34~0.69	60	0~82		6.01
Control group	Care as usual	22	0.97	0.78~1.16	80	71~86	0.02	2.88
	Waiting list/other	10	0.65	0.45~0.85	61	0~79		4.55
Target group	Adults	15	0.95	0.74~1.16	65	32~79	0.16	2.95
	Perinatal depression	7	0.67	0.44~0.90	84	67~91		4.39
	Other	10	0.97	0.60~1.35	80	60~88		2.88
Diagnosis	Depressive disorder	21	0.91	0.74~1.09	74	57~82	0.48	3.02
	Cut-off on scale	11	0.80	0.53~1.07	84	72~89		3.58
Manual	Adapted	14	0.74	0.56~0.93	80	65~87	0.06	3.92
	Not adapted	18	0.99	0.78~1.19	68	42~79		2.82
Type of therapy	CBT	22	0.85	0.69~1.01	75	60~82	0.71	3.35
	Other	10	0.91	0.63~1.19	76	50~86		3.10
Format	Individual	12	0.89	0.68~1.10	63	17~79	0.28	3.18
	Group	15	0.94	0.69~1.20	81	68~87		2.99
	Other	5	0.64	0.35~0.94	78	27~89		4.63

Note. BDI: Beck's Depression Inventory; CBT: Cognitive Behavioral Therapy; CI: Confidence Interval; HAM-D: Hamilton Rating Scale for Depression; NNT: Numbers-needed-to-be-treated; *N*comp: number of comparisons used for the calculation of the effect size; *p*: this p-value indicates whether the effect sizes between the subgroups differ significantly from each other.

[a)] Outliers were Chiang et al., 2015; Huang et al., 2015; Leung et al., 2013; Liu et al., 2009; Mukhtar et al., 2011; Nakimuli et al., 2015; Ngai et al., 2015; Qiu et al., 2013; Rahman et al., 2008.

[b)] Extreme outliers were defined as studies with an effect size larger than g=2.0: Chiang et al., 2015; Mukhtar et al., 2011; Qiu et al., 2013.

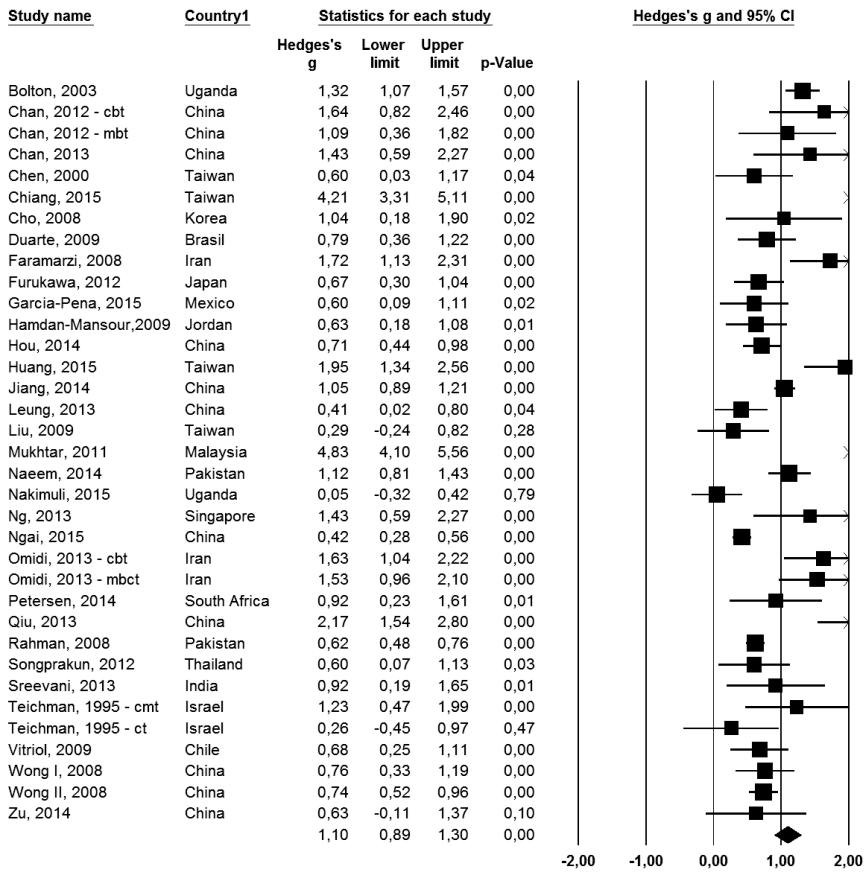

Figure 2. Forrest plot of effect sizes from randomized controlled trials on psychological treatments of depression in Non-Western countries

Visual inspection of the funnel plot, as well as Duval and Tweedie's trim and fill procedure, pointed at considerable publication bias. After adjustment for publication bias, the mean effect size was reduced from g=1.10 to g=0.73 (95% CI: 0.51 to 0.96; number of missed studies: 6). Egger's test also pointed at significant asymmetry of the funnel plot (p = 0.004; intercept: 2.42; 95% CI: 0.65 to 4.20).

In the subgroup analyses and all other analyses we excluded the extreme outliers, because these effect sizes were not credible and they influenced outcomes and heterogeneity considerably. In the subgroup analyses we found that risk of bias was significantly associated with the effect size, with the six comparisons with the lowest risk of bias (no risk of bias for any of the four items of the Risk of bias assessment tool) having an effect size of g=0.51 (95% CI: 0.34 to 0.69; NNT=6.01) compared to g=1.20 (95% CI: 0.84 to 1.56; NNT=2.29) in the studies with the highest risk of bias. We also found that type of control group was significantly associated with the effect size

(with care-as-usual control groups resulting in higher effect sizes than waiting list and other control groups). None of the other subgroup analyses resulted in significant differences between subgroups, and that included the region (East Asia, Middle East and North Africa, South Asia, other), the level of income of the country (high, upper middle, low/lower middle), and whether or not the treatment was adapted to the local situation.

We conducted a series of bivariate meta-regression analyses. In these analyses, we found no indication that the effect size was significantly associated with the GNI (coefficient: 0.00; 95% CI: -0.00 to 0.00; p=0.56), the number of treatment sessions (coefficient: 0.00; 95% CI: -0.04 to 0.04; p=1.00), and year of publication (coefficient: 0.00; 95% CI: -0.03 to 0.04; p=0.84).

Comparison between the effects of psychotherapy in Western and those in non-Western countries

We compared the 32 comparisons from non-Western countries with the 291 comparisons from Western countries (Table 3; extreme outliers with g>2.0 from studies in Western countries were also excluded from these analyses). We found that the effect sizes in Western countries (g=0.60; 95% CI: 0.55 to 0.64; I^2=59; 95% CI: 53 to 64; NNT=4.99) was significantly lower than in non-Western countries (p<0.001). We also examined the effect sizes in the different regions and found that the effect sizes differed significant across regions (p<0.001), with the lowest effect sizes in North America, Europe and Australia, and the highest in East Asia, South Asia and the Middle East and North Africa. We also found a significant difference across countries with different incomes, with the highest effect sizes in low and middle-income countries. In addition, we conducted a separate subgroup analysis in which we separated high-income countries into Western and non-Western countries (Table 3). We found that the 8 studies in high-income, non-Western countries resulted in an effect size of g=0.86 (95% CI: 0.48 to 123; NNT=3.30; I2=71; 95% CI: 24 to 84) compared to g=0.59 in Western countries (Table 2). A direct comparison between high-income countries in Western and non-Western countries did not indicate a significant difference (p=0.17), but this may have been related to the small number of studies from high-income non-Western countries.

We conducted a series of multivariate meta-regression analyses with the effect size as dependent variable (Table 4). In the first analysis, we included a dummy variable indicating whether the study was conducted in a Western or non-Western country, and also included other variables of the participants (a diagnosis of depression versus scoring above a cut-off on a self-report scale; the target group), the therapies (type, treatment format, number of sessions) and characteristics of the studies (type of control group and risk of bias). As can be seen in Table 4, whether the study was conducted in a Western or non-Western country remained a significant predictor of the effect size after adjusting for all other characteristics of the participants, interventions and studies (p<0.001).

Table 3. Psychotherapies for adult depression in Western and non-Western countries compared with control conditions: Hedges' g (N=323)

		*N*comp	*g*	95% CI	I^2	95% CI	*p*	NNT
Western vs non-Western	Western	291	0.60	0.55~0.64	59	53~64	<0.001	4.99
	Non Western	32	0.87	0.73~1.02	78	69~83		3.26
Region	North-America	165	0.67	0.59~0.74	61	53~67	<0.001	4.39
	Europe	107	0.51	0.45~0.57	47	32~58		6.01
	Australia	19	0.62	0.38~0.85	74	56~82		4.80
	East Asia	17	0.83	0.64~1.02	77	61~84		3.44
	Middle East	6	1.17	0.69~1.65	74	18~87		2.35
	South Asia	3	0.86	0.47~1.25	77	0~91		3.30
	Other	6	0.73	0.30~1.16	85	64~91		3.98
Income country	High	297	0.60	0.55~0.65	59	54~64	0.002	4.99
	Upper middle	20	0.92	0.74~1.11	76	61~83		3.06
	Low/lower middle	6	0.83	0.44~1.22	88	76~93		3.44
Income country [a) b)]	High - Western	289	0.59	0.55~0.64	58	53~63	0.003	5.08
	High – non-Western	8	0.86	0.48~1.23	71	24~84		3.30
	Upper middle	18	0.93	0.73~1.12	78	64~85		3.02
	Low/lower middle	6	0.83	0.44~1.22	88	76~93		3.44

Note. CI: Confidence Interval; NNT: Numbers-needed-to-be-treated; *N*comp: number of comparisons used for the calculation of the effect size; *p*: this p-value indicates whether the effect sizes between the subgroups differ significantly from each other.

[a)] In this subgroup analysis, we separated the high countries into Western and non-Western. One study was from Turkey, which is a Western country according to the World Bank, but is a upper middle income country. We left this study out of these analyses

[b)] The difference between Western and non-Western high-income countries (leaving out studies with other incomes was not significant (p=0.17), possibly because of low power.

Table 4. Standardized regression coefficients of characteristics of studies on psychological treatment of depression in Western and non-Western countries: Full multivariate metaregression analyses [a]

		Coeff	*SE*	*p*	Coeff	*SE*	*p*	Coeff	*SE*	*p*
Western vs non-Western countries		0.26	0.08	<0.001						
Region	North America				Ref.					
	Europe				-0.02	0.06	0.83			
	Australia				0.08	0.10	0.44			
	East Asia				0.17	0.11	0.11			
	Middle East				0.44	0.18	0.02			
	South Asia				0.44	0.20	0.03			
	Other				0.25	0.16	0.11			
Income country	High							Ref.		
	Low/lower middle							0.43	0.15	0.004
	Upper middle							0.31	0.10	0.002
Diagnosis vs cut-off		-0.02	0.05	0.63	-0.01	0.05	0.88	-0.01	0.05	0.83
Target group	Unselected adults	Ref.			Ref.			Ref.		
	Older adults	-0.05	0.07	0.52	-0.04	0.08	0.56	-0.04	0.07	0.55
	Women with PPD	-0.04	0.08	0.65	-0.04	0.08	0.61	-0.04	0.08	0.58
	General medical dis	0.04	0.07	0.57	0.04	0.07	0.60	0.04	0.07	0.53
	Other	0.05	0.07	0.45	0.03	0.07	0.64	0.06	0.07	0.38
Type	CBT	Ref.			Ref.			Ref.		
	IPT	-0.08	0.09	0.39	-0.07	0.09	0.44	-0.09	0.09	0.33
	PST	-0.03	0.10	0.75	-0.02	0.10	0.84	-0.03	0.09	0.73
	Supportive	0.03	0.11	0.81	0.05	0.11	0.67	0.05	0.11	0.65

continued

Table 4. Standardized regression coefficients of characteristics of studies on psychological treatment of depression in Western and non-Western countries: Full multivariate metaregression analyses [a] (continued)

		Coeff	*SE*	*p*	Coeff	*SE*	*p*	Coeff	*SE*	*p*
	Other	0.02	0.06	0.75	0.03	0.06	0.64	0.02	0.06	0.72
Format	Individual	Ref.			Ref.			Ref.		
	Group	-0.10	0.06	0.08	-0.10	0.06	0.07	-0.12	0.06	0.03
	Guided self-help	0.05	0.07	0.53	0.04	0.08	0.57	0.03	0.07	0.67
	Other/mixed	-0.17	0.10	0.09	-0.15	0.10	0.13	-0.18	0.10	0.07
Number of sessions (continuous)		-0.00	0.01	0.68	0.00	0.01	0.54	0.00	0.01	0.65
Risk of bias (continuous)		-0.12	0.02	<0.001	-0.12	0.02	<0.001	-0.12	0.02	<0.001
Control group	Waiting list	Ref.			Ref.			Ref.		
	Care as usual	-0.09	0.06	0.14	-0.10	0.06	0.13	-0.11	0.06	0.08
	Other	-0.21	0.07	<0.01	-0.23	0.07	<0.001	-0.23	0.07	<0.001
Intercept		1.01	0.10	<0.001	1.00	0.10	<0.001	1.03	0.10	<0.001
R^2 analog		0.36			0.36			0.38		

[a)] Extreme outliers ($g \geq 2$) were excluded from these analyses

Note. CBT: Cognitive Behavioral Therapy; Coeff: Regression Coefficient; HAM-D: Hamilton Rating Scale for Depression; IPT: Interpersonal Psychotherapy; *p*: this p-value indicates whether the regression coefficient of the subgroups differ significantly from the reference group; PST: Problem Solving Therapy; Ref: Reference group; SE: Standard Error

In the second meta-regression analysis we used the same predictors, except that we replaced the dummy variable that indicated that the study was conducted in Western vs. a non-Western country was removed, and instead we added the variable indicating the region where the study was conducted. We found that studies in the Middle East and North Africa, and South Asia had significantly higher effect sizes than the reference group (studies from the United States).

In the third meta-regression analysis, we included the income of the country as predictor, and we found that both studies conducted in upper middle (p=0.002) and studies in low/lower middle countries p=0.004) had significantly higher effect sizes than those in high-income countries, while adjusting for all other variables.

We did not include the dummy indicating Western versus non-Western countries, the regions and the income level in one analysis, because the overlap across these variables was considered too large.

To avoid overfit of the meta-regression models, we repeated these three meta-regression analyses, with a (manual) stepwise backward elimination of the least significant predictor until only significant predictors remained in the model. The results of these parsimonious analyses are presented in Table 5. As can be seen, in all three models risk of bias and type of control group remained significant, and it was found that the dummy indicating Western versus non-Western countries, the regions and the income level remained significant.

DISCUSSION

We found that psychotherapies for depression that have been developed mostly in Western countries are also effective in non-Western countries. We even found indications that these therapies may be more effective in non-Western than in the Western countries where they were developed. This finding remained significant in multivariate meta-regression analyses in which we controlled for characteristics of the participants, the interventions and the studies.

We classified these studies in different ways. In one analysis in which we simply differentiated between Western and non-Western countries. In these analyses we found that the studies in non-Western countries had better outcomes than those from Western countries. In another analysis we categorized the countries into the major regions of the world according to the World Bank. In these analyses we found that the effect sizes were especially high in the Middle East and North Africa, and in South Asia, although the lack of statistical significance for other regions may be caused by lack of power due to the small samples of studies. We also classified the countries according to their income (high, upper middle and low/lower middle). We found that studies in upper middle and low/lower middle income countries resulted in significantly higher effect sizes than studies in high-income countries. Studies from non-Western high-income countries resulted in effect sizes that were comparable to those from middle and low/lower middle-income countries. These effect sizes from non-Western high-income countries were larger than those

Table 5. Standardized regression coefficients of characteristics of studies on psychological treatment of depression in Western and non-Western countries: Parsimonious multivariate meta-regression analyses

		Coeff	*SE*	*p*	Coeff	*SE*	*p*	Coeff	*SE*	*p*
Western vs non-Western countries		0.23	0.07	<0.001						
Region	North America				Ref.					
	Europe				-0.01	0.06	0.91			
	Australia				0.08	0.10	0.42			
	East Asia				0.13	0.10	0.21			
	Middle East				0.43	0.17	0.01			
	South Asia				0.40	0.19	0.04			
	Other				0.22	0.15	0.15			
Income country	High							Ref.		
	Low/lower middle							0.36	0.14	0.01
	Upper middle							0.24	0.09	0.01
Risk of bias (continuous)		-0.10	0.02	<0.001	-0.10	0.02	<0.001	-0.11	0.02	<0.001
Control group	Waiting list	Ref.			Ref.			Ref		
	Care as usual	-0.12	0.05	0.02	-0.12	0.05	0.02	-0.13	0.05	0.02
	Other	-0.23	0.06	<0.001	-0.25	0.06	<0.001	-0.25	0.06	<0.001
Intercept		0.98	0.05	<0.001	0.98	0.06	<0.001	0.99	0.05	<0.001
R^2 analog		0.37			0.37			0.38		

Note. Coeff: Regression Coefficient; *p*: this p-value indicates whether the regression coefficient of the subgroup differs significantly from the reference group; Ref: Reference group; SE: Standard Error

from Western high-income countries, but this difference was not significant, possibly because of low statistical power.

It is not clear why the studies in non-Western countries seemed to have better outcomes. It is possible that these therapies simply work better in (some) non-Western countries, but it is not clear why that would be the case. Another explanation could be that most studies in non-Western countries had care-as-usual control groups and that care-as-usual in these cases simply means they get no treatment at all, while in Western countries care-as-usual implies that patients have access to several treatments, like regular care provided by general practitioners or specialized mental health services. This is supported by our finding that the effects in high-income non-Western countries (mainly in East Asia) did not significantly differ from those in Western countries, although that may be the result of low power. Another explanation could be that the quality of the studies conducted in non-Western countries was not optimal. Risk of bias was low in only 6 of the 37 included comparisons, and these studies with low risk of bias had considerably lower effect sizes than the ones with higher risk of bias, and these lower effect sizes are very comparable to the ones found in Western countries.

We did not find indications that a specific adaptation of the treatment to the context where the therapy was conducted was associated with better outcomes. This finding should be considered with caution, because the description of the intervention was very brief in most papers, thus it cannot be excluded that the interventions were still adapted without mentioning this in the paper.

These findings do suggest that psychotherapies that were developed in Western countries can probably be offered to patients in non-Western countries and that these therapies may be effective in these countries. That suggests that these therapies can possibly be implemented in non-Western countries when sufficient resources are available and without culturally adapting them. It has been argued recently that an investment in mental health care in low-and middle income countries has considerable economic support with a beneficial return on investment (Chisholm et al., 2016). Because we found no indication that the effects are associated with the treatment format, it would be possible to introduce low intensity interventions as a first line treatment, because these are easier and cheaper to implement than high intensity interventions.

This study has several limitations that have to be taken into account when interpreting the results. One important limitation is that we may have missed studies because our searches mainly focused on Western databases, and we have missed studies published in other languages that are not directly accessible. That implies that our results may be distorted because of bias in the selection of studies. Another important limitation is that the quality of most of the included studies was not optimal and only a handful of studies had a high quality. Furthermore, these studies found considerably smaller effect sizes than the other studies, suggesting that the true effects are probably smaller than we found. However, after adjustment for study quality and other characteristics of the studies, studies in non-Western countries were still more effective

than those in Western countries. Another limitation is that most studies in non-Western counties were conducted in a selected sample of countries in Asia, and only few in Africa and South-America.

Despite these limitations this study suggests that psychological treatments that were developed in Western countries may or may not be more effective in non-Western countries, but they are probably no less effective and can therefore also be used in non-Western countries, regardless of the income level of that country.

04

CHAPTER 5

ECONOMIC EVIDENCE FOR THE CLINICAL MANAGEMENT OF MAJOR DEPRESSIVE DISORDER: A SYSTEMATIC REVIEW AND QUALITY APPRAISAL OF ECONOMIC EVALUATIONS ALONGSIDE RANDOMIZED CONTROLLED TRIALS

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ABSTRACT

Aims:
The aim of this systematic review of economic evaluations alongside randomised controlled trials (RCTs) was to provide a comprehensive overview of the evidence concerning cost-effectiveness analyses (CEA) of common treatment options for major depression.

Methods:
An existing database was used to identify studies reporting cost-effectiveness results from RCTs. This database has been developed by a systematic literature search in the bibliographic databases of PubMed, PsychINFO, Embase and Cochrane library from database inception to December 2014. We evaluated the quality of economic evaluations using a 10-item short version of the Drummond checklist. Results were synthesized narratively. The risk of bias of the included RCTs was assessed, based on the Cochrane risk of bias assessment tool.

Results:
Fourteen RCTs were included from the 5,580 articles screened on titles and abstracts. The methodological quality of the health economic evaluations was relatively high and the majority of the included RCTs had low risk of bias in most of Cochrane items except blinding of participants and personnel. Cognitive Behavioural Therapy (CBT) was examined in seven trials as part of a variety of treatment protocols and seems cost-effective compared to pharmacotherapy in the long-term. However cost-effectiveness results for the combination of psychotherapy with pharmacotherapy are conflicting and should be interpreted with caution due to limited comparability between the examined trials. For several treatments, only a single economic evaluation was reported as part of a clinical trial. This was the case for comparisons between different classes of antidepressants, for several types of psychotherapy (behavioural activation, occupational therapy, interpersonal psychotherapy, short-term psychotherapy, psychodynamic psychotherapy, rational emotive behavioural therapy, solution focused therapy), and for transcranial magnetic stimulation versus electroconvulsive therapy. The limited evidence base for these interventions means generalisations, based on economic evaluation alongside clinical trials, cannot easily be made.

Conclusions:
There is some economic evidence underpinning many of the common treatment options for major depression. Wide variability was observed in study outcomes, probably attributable to differences in population, interventions or follow-up periods. For many interventions, only a single economic evaluation alongside clinical trials was identified. Thus, significant economic evidence gaps remain in the area of major depressive disorder.

INTRODUCTION

Major depressive disorder (MDD) is one of the most common conditions worldwide and is associated with high risk of mortality and morbidity. Lifetime depression prevalence ranges from 3% in Japan to 17% in the US, while the majority of countries fall within the range of 8% to 12% (Andrade et al., 2003; Kessler, Chiu, Demler, & Walters, 2005). MDD has severe economic consequences for individuals and society arising out of increased healthcare utilisation, caregiver burden and labour force productivity losses (Cuijpers, Beekman, & Reynolds, 2012; Lepine & Briley, 2011). Furthermore, MDD is a major cause of disease burden throughout the world and is one of the priority conditions examined under the Research Agenda for Health Economic Evaluation (RAHEE) project implemented by the World Health Organization (WHO) (Tordrup, Attwill, Crosby, & Bertollini, 2015; Tordrup & Bertollini, 2014). The objective of the RAHEE project is to identify health economic research priorities based on availability of economic evidence for selected conditions. The present review arose as part of this project.

There is ample evidence for the therapeutic effectiveness of several forms of therapy in treating MDD. For instance, several systematic reviews have examined the effects of pharmacotherapy and psychotherapy and have demonstrated that both therapeutic options are effective in treating depressive disorders in both the short and the long term (Cuijpers, Dekker, Hollon, & Andersson, 2009; Cuijpers, van Straten, et al., 2008b; Cuijpers, van Straten, van Oppen, & Andersson, 2008; Karyotaki et al., 2016). Moreover, research has shown that other treatment alternatives, such as transcranial magnetic stimulation (rTMS), can be effective in treating the symptoms of MDD (Lee, Blumberger, Fitzgerald, Daskalakis, & Levinson, 2012). Considering the rising health care costs associated with the treatment of MDD, it is important to further examine the cost-effectiveness of common treatment options, however only a few systematic reviews have touched upon this.

Grochtdreis et al. (2015) performed a systematic review of studies examining the cost-effectiveness of collaborative care compared to usual care in patients with depression. The authors found studies were inconsistent in their quality and results, and conclusions were ambiguous depending on willingness to pay. Incremental cost per Quality Adjusted Life Year (QALY) ranged from dominance to US$ 874,562 Purchasing Power Parity (Grochtdreis et al., 2015). Furthermore, Rabheru (2012) searched for cost-effectiveness evidence of maintenance electroconvulsive therapy (M-ECT) in patients who had responded to ECT but found no trials reporting cost-effectiveness in a maintenance setting since 1997. In the same year, Lee et al. (2012) published a review on the clinical and cost-effectiveness evidence of Transcranial Magnetic Stimulation (TMS) in the treatment of resistant MDD. The authors examined four studies, which were in disagreement on the cost-effectiveness of TMS versus ECT. To the best of our knowledge there are no recent (carried out in the past ten years) systematic reviews on the cost-effectiveness of psychotherapy or the combination of pharmacotherapy and psychotherapy in patients with MDD.

Given the limited evidence on the cost-effectiveness of treatments for major depression in existing reviews, the present systematic review of randomized controlled trials seeks to provide a comprehensive overview of the cost-effectiveness of the most common treatment options for MDD. We aimed to identify evidence gaps, as well as highlight the methodological challenges inherent in synthesising the available evidence.

METHODS

Search Strategy

We screened an existing database that was developed to identify all randomized controlled trials on cost-effectiveness outcomes in the treatment of common mental disorders (depression and anxiety disorders). This database has been used in a recently submitted paper, reporting a global return on investment analysis on mental health for depression and anxiety disorders (Chisholm et al., 2016). We built the database employing a systematic literature search in PubMed, PsychINFO, Embase and Cochrane library from database inception to December 2014. In these searches, various terms covering economic evaluation and common mental disorders were used in different combinations, using both index and free terms. A full search string for PubMed is provided Appendix A. In total, 6,347 references are included in the database and were examined for eligibility in the present review (2,203 from PubMed, 321 from PsychINFO, 2,046 from . Embase and 1,777 from the Cochrane library). In addition to this database, we conducted a separate search in PubMed for verification purposes. Resulting titles and abstracts were screened for eligibility and full texts were retrieved and examined for inclusion. Flow chart 1 shows the study selection process.

Inclusion Criteria

Participants: Individuals with moderate or severe MDD (as defined in individual studies). No age or country restriction was applied

Intervention: Treatment options for MDD - psychotherapy, pharmacotherapy, combined psychotherapy with pharmacotherapy, physical treatments (electroconvulsive therapy and transcranial magnetic stimulation)

Comparison: Control comparison conditions (treatment as usual or pill placebo); or active comparison conditions (common treatment options for MDD, as described above)

Outcomes: We included full economic evaluations reporting outcomes on cost-benefit, cost-effectiveness and cost-utility. We also considered cost-minimisation studies of interventions with identical effectiveness (a special case of cost-effectiveness), and cost-consequence studies where one intervention was less costly and more effective (equivalent to a dominant intervention in a cost-effectiveness study).

Study design: RCTs

Exclusion criteria

Studies were excluded if they did not integrate cost- and effectiveness analyses, e.g. cost-consequence or cost-minimisation studies, except as specified above. Moreover, we excluded collaborative care interventions since this topic has already been covered by a recent systematic review (Grochtdreis et al., 2015). Modelling studies were excluded due to methodological differences compared to RCT-based economic evaluations. Further, studies were excluded if the language was not English. Finally, we did not search for unpublished data because it was out of the scope of the present systematic review.

Quality Assessment of economic evaluations

We assessed the methodological quality of the economic evaluations based on the Drummond 10-item checklist (Drummond, 2005). For each of the 10 items, studies were scored as 'yes', 'no', 'cannot tell' or 'not applicable', the latter being used for items that were not applicable to certain studies. One author (C.B.) completed the checklist and another reviewed it (E.K.). Disagreement was resolved through discussion.

Risk of bias assessment

Furthermore, we assessed the validity of the included studies according to the Cochrane Collaboration's Risk of bias assessment tool (Higgins et al., 2011; Higgins & Green, 2011). This tool examines the following domains of possible bias: a) selection bias: systematic differences between groups in baseline characteristics due to inadequate random sequence generation or allocation concealment, b) performance bias: systematic differences between the groups in the treatment provided due to the absence of blinding of participants and personnel, c) detection bias: systematic differences between the groups in how outcomes were assessed and determined due to the absence of blinding of outcome assessors, d) attrition bias: systematic differences between groups in study dropout (incomplete outcome data), e) reporting bias: systematic differences between reported and unreported results (selective reporting), f) other bias: bias due to other issues (Higgins et al., 2011; Higgins & Green, 2011).

Data extraction and management

Two authors (E.K and D.T) extracted independently the following data: authors' names, study setting, major depression diagnosis status, type and duration of the therapy, type of control groups and economic perspective and outcomes. This information is summarized in table 1. Data from the included studies are combined narratively and are presented in the following section. This narrative description presents the main characteristics of the economic evidence. All costs were inflated to 2014 US$ Purchasing Power Parity using OECD and World Bank country specific Consumer Price Index statistics and currency conversion rates (Organisation for Economic Cooperation and Development, 2016a, 2016b; World Bank, 2015). 2014 US$ PPP values are given throughout the manuscript, with original currencies and values in [brackets].

RESULTS – DATA SYNTHESIS

Study characteristics

Across the 14 included RCTs (fig. 1), outpatients were recruited mainly through clinical samples (n = 12), while two studies recruited participants through both community and clinical referrals. The included studies were conducted in six different countries: Finland (n = 1), Romania (n = 1), the Netherlands (n = 3), Japan (n=1), the United Kingdom (n = 5) and the United States (n = 3). Time horizons for economic outcomes were 2 to 36 months. The included RCTs examined eight types of psychotherapeutic interventions: behavioural activation (BA; n = 1 study), cognitive behavioural therapy (CBT; n = 7 studies), interpersonal psychotherapy (IPT; n = 1 study), occupational therapy (OT; n = 1 study), psychodynamic psychotherapy (PDT; n = 1 study), psychoeducation (PEP; n = 2 studies), rational emotive behavioural therapy (REBT; n = 1 study) and solution focused therapy (SFT; n = 1 study), while the included pharmacotherapeutic trials examined mostly antidepressants from the cluster of selective serotonin reuptake inhibitors (SSRIs). Finally, one trial examined the effects of transcranial magnetic stimulation compared with electroconvulsive therapy. Studies targeting absolute efficacy used treatment as usual (TAU) or pill placebo as control comparison condition (n = 8 studies). Table 1 presents a summary of study characteristics.

Quality assessment of economic evaluations

The overall methodological quality of the economic evaluations was relatively good, but varied among studies. The mean relative value of the methodological quality criteria fulfilled was 9.7 out of 12 (see Table 2). The minimum relative value of criteria fulfilled was 8 (Knapp et al., 2008) and the maximum value of criteria met was 11 (Domino et al., 2008, Hollinghurst et al., 2014, Lynch et al., 2011, Maljanen et al., 2012). All studies included a well-defined research question, reported on the effectiveness of the programme or service concerned, identified all relevant costs and consequences for each alternative, measured costs and consequences accurately, and valued the cost credibly. All studies except for one (in brackets) included a comprehensive description of the competing alternatives (Wade et al., 2008), valued the consequences credibly (Byford et al., 2007), performed an incremental analysis of costs and consequences of alternatives (Knapp et al., 2008), and included a presentation and discussion of study results that covered all issues of concern to users (Knapp et al., 2008). Only three studies reported on adjusting cost and consequences for differential timing (Byford et al., 2007, Domino et al., 2008, Maljanen et al., 2012). Five studies did not make allowances for uncertainty in the estimation of costs (Bosmans et al., 2007, Domino et al., 2008, Ekers et al., 2011, Revicki et al., 2005, Sava et al., 2009). Only three studies allowed for uncertainty in the estimation of consequences (Domino et al., 2008, Hollinghurst et al., 2014, Lynch et al., 2011).

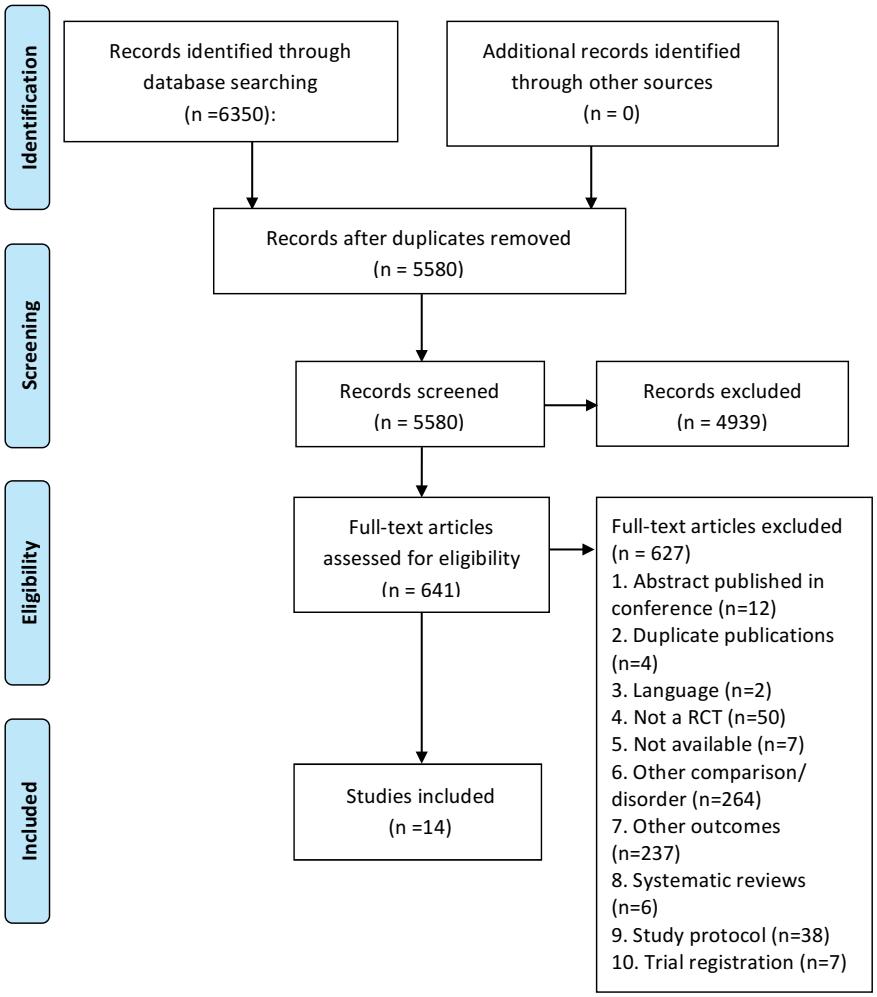

Figure 1 PRISMA flow chart of study selection process

Table 1. Study Characteristics

Study	Recruitment	Diagnosis	Interventions	N patients per intervention	FU (months)	Results on cost-effectiveness outcomes	Country	Perspective
Moderate major depressive disorder								
Psychotherapeutic interventions vs. other types of psychotherapeutic interventions or control groups								
Schene, Koeter, Kikkert, Swinkels, and McCrone (2007)	Clinical setting	Moderate MDD (DSM-IV)	▪ OT & TAU ▪ TAU	▪ 30 ▪ 32	42	Compared with TAU: ▪ OT&TAU did not improve depression outcomes ▪ OT&TAU had a 75·5% probability of being cost-effective (higher net benefit at an average wage value of US$ 44.74 [US$36.88]) compared to TAU alone. ▪ OT&TAU resulted in more hours worked in the first 18 months	NL	Societal
Shimodera et al. (2012)	Clinical setting	Moderate MDD (DSM-IV)	▪ Maintenance TAU & family PEP ▪ Maintenance TAU	▪ 24 ▪ 30	9	▪ The total costs were US$ 1,897 [US$1,842] for maintenance TAU & family PEP compared to US$ 2,717 [US$2,638] for maintenance TAU group. Differences between groups were not significant (p=0.509) ▪ Maintenance TAU & family PEP had a 90% probability of being cost-effective compared to maintenance TAU alone if the decision maker is willing to pay US$ 21 [US$20] for 1 additional day free of relapse	JP	Health system

continued

Table 1. Study Characteristics (continued)

Study	Recruitment	Diagnosis	Interventions	N patients per intervention	FU (months)	Results on cost-effectiveness outcomes	Country	Perspective
Stant et al. (2009)	Clinical setting	Moderate MDD (DSM-IV)	▪ CBT-enhanced PEP ▪ PEP ▪ Psychiatrist-enhanced PEP ▪ TAU	▪ 36 ▪ 97 ▪ 33 ▪ 61	36	▪ The mean total intervention costs were: o CBT-enhanced PEP: US$ 12,506 [€ 9,254] o PEP: US$ 13,265 [€ 9,816] Psychiatrist-enhanced PEP: US$ 13,303 [€ 9,844] o TAU: US$ 11,081 [€ 8,200] ▪ No significant differences were observed in QALY gains ▪ Up to a willingness-to-pay of US$ 405 [€ 300] for 1 additional depression free day, TAU was most cost-effective. Above this threshold, CBT-enhanced PEP was most cost-effective closely followed by psychiatrist-enhanced PEP.	NL	Societal
Ekers et al. (2011)	Clinical setting	Moderate Depression (ICD-10)	▪ BA ▪ TAU	▪ 24 ▪ 23	3	▪ BA yielded significantly higher QALY gain of 0.20 (95% CI 0.01 to 0.39, p=0.042) ▪ ICER of US$ 8,301 [£ 5,756] per QALY for BA at 3 months ▪ 97% probability that BA is cost-effective compared to TAU at a threshold value of US$ 28,843 [£ 20,000]	UK	Health System
Maljanen et al. (2012)	Clinical setting	Moderate MDD (DSM-IV)	▪ S-PDT ▪ S-SFT	▪ 101 ▪ 97	12	No significant differences in costs or outcomes were observed ▪ The mean total direct costs in the S-PDT group (US$ 1,946 [€ 1,791]) were 16% lower than the mean total direct costs in the S-SFT group (US$ 2,322 [€ 2,137]). Differences between groups were not significant (p>0.05) ▪ Symptoms were significantly reduced in both interventions, but with no significant differences between the two	FI	Societal

continued

Table 1. Study Characteristics (continued)

Study	Recruitment	Diagnosis	Interventions	N patients per intervention	FU (months)	Results on cost-effectiveness outcomes	Country	Perspective
Bosmans, Brook, et al. (2007)	Clinical setting	Moderate MDD (PRIME-MD)	▪ IPT ▪ TAU	▪ 69 ▪ 74	12	No significant differences in mean total cost or remission were observed ▪ IPT group experienced 6% less remission (MADRS) compared to TAU at 12 months ▪ Total costs (direct & indirect) were on average non-significantly higher (US$ 1,039 [€ 769]) for IPT. ▪ This resulted in a negative ICER of US$ -177 [€ -131] for IPT compared with TAU, with cost-effect pairs mostly distributed near the origin and in all four quadrants of the cost-effectiveness plane	NL	Societal
Combinations of and comparisons between psychotherapeutic interventions and pharmacotherapy								
Domino et al. (2008); (2009)	Clinical setting	Moderate MDD (DSM-IV)	▪ CBT ▪ ADM (SSRI) ▪ CBT & ADM (SSRI) ▪ Placebo	▪ 111 ▪ 109 ▪ 107 ▪ 112	3, 9	▪ ICER's over placebo at 12 weeks: o CBT: US$ 11,866,556 [US$ 9,210,622] o ADM: US$ 30,582 [US$ 23,737] o CBT & ADM: US$ 158,652 [US$ 123,143] ▪ CBT & ADM had more than 90% probability (at a threshold of US$ 128,836 [US$ 100,000]) of being more cost-effective than ADM alone at 36 weeks. ▪ CBT is not likely to be more cost-effective than ADM alone at 36 weeks.	US	Societal

continued

Table 1. Study Characteristics (continued)

Study	Recruitment	Diagnosis	Interventions	N patients per intervention	FU (months)	Results on cost-effectiveness outcomes	Country	Perspective
Lynch et al. (2011)	Clinical setting	Moderate MDD (DSM-IV)	▪ SSRI ▪ SSRI & CBT	▪ 168 ▪ 166	6	Combined treatment resulted in 8.3 additional depression free days (p=0.03) ICERs: ▪ US$ 221 [US$ 188] (95%CI US$ -26 [US$ -22] to US$ 1,896 [US$ 1,613]) per depression free day ▪ US$ 167 [US$ 142] (95%CI US$ -16 [US$ -14] to US$ 2,973 [US$ 2,529]) per depression improvement day ▪ US$ 92,812 [US$ 78,948] (95%CI US$ -10,840 [US$ -9,221] to US$ 796,418 [US$ 677,448]) per QALY ▪ 61% probability that combined treatment is cost- effective at a willingness to pay of US$ 117,561/QALY [US$ 100,000/QALY]	US	Societal
Byford et al. (2007)	Clinical setting	Moderate MDD (DSM-IV)	▪ CBT & SSRIs ▪ SSRIs	▪ 105 ▪ 103	7	No significant differences in cost or QALY effects were observed. ▪ For CBT & SSRI compared with SSRI alone, the ICER is US$ 4,687 [£ 2,873] per unit increase in HoNOSCA (higher scores indicate worsening of symptoms) ▪ There is only 25% probability that CBT & SSRI is more cost-effective than SSRI alone at a threshold value of US$ 81,577 [£50,000]	UK	Societal

continued

Table 1. Study Characteristics (continued)

Study	Recruitment	Diagnosis	Interventions	N patients per intervention	FU (months)	Results on cost-effectiveness outcomes	Country	Perspective
Sava, Yates, Lupu, Szentagota and David (2009)	Community & Clinical setting	Moderate MDD (DSM-IV)	▪ CBT ▪ REBT ▪ SSRI	▪ 56 ▪ 57 ▪ 57	6	▪ Both CBT and REBT were more cost-effective per depression free day gained per month compared to SSRI: o CBT median: US$ 70.63 [US$ 26.44] o REBT median: US$ 63.50 [US$ 23.77] o SSRI median: US$ 93.31 [US$ 34.93] ▪ Both CBT and REBT exhibited better cost-utility compared to SSRIs o CBT: US$ 4,375 [US$ 1,638] o REBT: US$ 4,632 [US$ 1,734] o SSRI: US$ 6,109 [US$ 2,287].	RO	Societal
Revicki et al. (2005)	Clinical setting	Moderate MDD (DSM-IV)	▪ SSRI ▪ CBT ▪ TAU	▪ 88 ▪ 90 ▪ 89	12	▪ SSRI resulted in more depression-free days (mean, 39.7; 95% CI, 12.9 to 66.5) than the CBT group (mean, 25.80; 95% CI, 0.04-51.50) compared to TAU. ▪ The outpatient and medication costs were US$ 32.49 [US$ 24.65] per additional depression-free day for pharmacotherapy and US$ 35.64 [US$ 27.04] for CBT vs. TAU. Total cost (incl. inpatient) was approximately double. ▪ ICER's including total costs (outpatient+inpatient+medication) were US$ 39,570/QALY [US$ 30,023/QALY] for pharmacotherapy and US$ 49,514 [US$ 37,568] for CBT	US	Health System

Continued

Table 1. Study Characteristics (continued)

Study	Recruitment	Diagnosis	Interventions	N patients per intervention	FU (months)	Results on cost-effectiveness outcomes	Country	Perspective
Direct comparison between antidepressant agents								
Wade et al. (2008)	Clinical setting	Moderate MDD (DSM-IV)	▪ SSRIs ▪ SNRIs	▪ 144 ▪ 151	6	▪ Total costs were significantly lower (p<0.05) for the SSRI (US$ 294 [£ 188]) compared to the SNRI (US$ 522 [£ 334]) ▪ The SSRI was also more effective in terms of SDS score reduction, with a difference of 2.4 (95% CI 0.4, 4.1) against the SNRI ▪ Mean sick leave duration was significantly shorter with the SSRI (30.7 days vs 62.2 days; p = 0.007)	UK	Societal
Severe and refractory major depressive disorder								
Electroconvulsive therapy and repetitive transcranial magnetic stimulation								
Knapp et al. (2008)	Clinical setting	Severe MDD (Diagnostic interview not specified)	▪ ECT ▪ rTMS	▪ 22 ▪ 24	7	▪ ECT was initially more effective than rTMS with 59% vs 17% of patients achieving remission, but no differences were observed after 6 months follow-up (p=0.93). Total costs were lower for ECT than for rTMS (p=0.04) ▪ At a willingness-to-pay of US$ 826 [£ 500] per unit of symptom improvement (HSRD), there is a 98% probability rTMS is cost-effective compared with ECT. However at a willingness-to-pay of zero per unit of improvement, the probability is 24%. ▪ At a willingness-to-pay of US$ 49,583 [£ 30,000] per QALY, the probability of rTMS being cost-effective compared with ECT is less than 20%	UK	Both

Continued

Table 1. Study Characteristics (continued)

Study	Recruitment	Diagnosis	Interventions	N patients per intervention	FU (months)	Results on cost-effectiveness outcomes	Country	Perspective
Addition of CBT								
Hollinghurst et al. (2014)	Clinical setting	Treatment resistant MDD (ICD-10)	▪ CBT & TAU ▪ TAU	▪ 234 ▪ 235	12	▪ CBT & TAU resulted in higher QALY gains of 0.057 (95% CI 0.015–0.099; p<0.05) corresponding to 21 days a year of good health ▪ The CBT & TAU group compared with TAU incurred a cost per QALY of US$ 20,817 [£ 14,911], corresponding to a probability of 74% that the intervention is cost-effective at a threshold value of US$ 27,922 [£20,000]	UK	Health System

Abbreviations: ADM: Antidepressant medication; BA: Behavioural Activation; CI: Confidence intervals; CI: Confidence Intervals; DSM: Diagnostic and Statistical manual of mental disorders; ECT: Electroconvulsive therapy; FI: Finland; FU: Follow up;HoNOSCA: Heath of the Nation Outcome Scale for children and adolescents; ICD: International Classification of diseases; ICER: Incremental Cost Effectiveness Ratio; IPT: Interpersonal Psychotherapy; MADRS: Montgomery Asberg Depression Scale; MDD: Major Depressive Disorder; n: number; OT: Occupational Therapy;PEP: Psychoeducation Programmme; PRIME-MD: PRIMary care Evaluation of Mental Disorders; QALY: Quality Adjusted Life Years; REBT: Rationale Emotive Behavioral Therapy; RO: Romania; rTMS: Transcranial Magnetic Stimulation; S-PDT: Short-term Psychodynamic therapy; S-SFT: Short-term Solution-focused therapy; SD: Standard Deviation; SNRIs: Serotonin Norepinephrine Reuptake Inhibitors; SDS: Sheehan Disability Scale; SSRIs: Selective Serotonin Reuptake Inhibitors; TAU: Treatment as Usual; UK: United Kingdom; US: United States; WEB: Psychiatric services through Webcam

Table 2. Quality assessment with the 10-item Drummond checklist

Checklist

1. Was a well-defined question posed in answerable form?
2. Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where, and how often)?
3. Was the effectiveness of the programme or services established?
4. Were all the important and relevant costs (a) and consequences (b) for each alternative identified?
5. Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, lost work-days, gained life years)?
6. Were the cost (a) and consequences (b) valued credibly?
7. Were costs and consequences adjusted for differential timing?
8. Was an incremental analysis of costs and consequences of alternatives performed?
9. Was allowance made for uncertainty in the estimates of costs (a) and consequences (b)?
10. Did the presentation and discussion of study results include all issues of concern to users?

Study	1	2	3	4		5	6		7	8	9		10
				a	b		a	b			a	b	
Bosmans et al. (2007)	✓	✓	✓	✓		✓	✓	✓	0	✓	x	x	✓
Byford et al. (2007)	✓	✓	✓	✓		✓	✓	0	X*	✓	✓	x	✓
Domino et al. (2008); Domino et al. (2009)	✓	✓	✓	✓		✓	✓	✓	X*	✓	x	✓	✓
Ekers et al. (2011)	✓	✓	✓	✓		✓	✓	✓	0	✓	x	x	✓
Hollinghurst et al. (2014)	✓	✓	✓	✓		✓	✓	✓	0	✓	✓	✓	✓
Knapp et al. (2008)	✓	✓	✓	✓		✓	✓	✓	0	0	✓	x	0
Lynch et al. (2011)	✓	✓	✓	✓		✓	✓	✓	0	✓	✓	✓	✓
Maljanen et al. (2012)	✓	✓	✓	✓		✓	✓	✓	X*	✓	✓	X	✓
Revicki et al. (2005)	✓	✓	✓	✓		✓	✓	✓	0	✓	x	x	✓
Sava et al. (2009)	✓	✓	✓	✓		✓	✓	✓	0	✓	X	X	✓
Schene et al. (2007)	✓	✓	✓	✓		✓	✓	✓	0	✓	✓	X	✓
Shimodera et al. (2012)	✓	✓	✓	✓		✓	✓	✓	0	✓	✓	X	✓
Stant et al. (2009)	✓	✓	✓	✓		✓	✓	✓	x	✓	✓	x	✓
Wade et al. (2008)	✓	0	✓	✓		✓	✓	✓	0	✓	✓	x	✓

Note: yes ✓, no X, explanation is given why costs and consequences are not discounted X*, cannot tell 0

Risk-of-bias assessment

With regard to risk-of-bias assessment, the majority of the included trials reported an adequate random sequence generation (11/14). The allocation was concealed in six out of the fourteen included RCTs while the remainder reported inadequate information to permit judgement. Blinding of personnel and participants was possible in only one of the included studies and incomplete outcome data were adequately addressed by eleven included RCTs. Finally the vast majority of the included trials were rated as free from selective outcome reporting bias (13/14) and other sources of bias (14/14) (Fig. 2.).

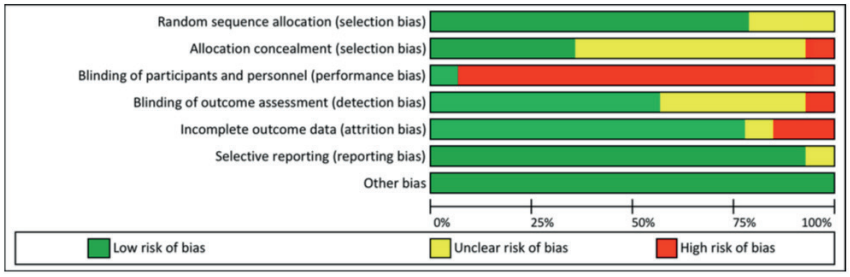

Figure 2. Risk of bias assessment.

Moderate major depressive disorder

Psychotherapeutic interventions vs. other types of psychotherapeutic interventions or control groups

One study examined the cost-effectiveness of psychotherapeutic interventions targeting work related outcomes (e.g. productivity losses). Schene et al. (2007) found that adding occupational therapy (OT) to treatment as usual (TAU) did not improve depression outcomes, but did result in a significant reduction of workdays lost over 18 months. Net benefit was calculated as the "value of work" (hourly wages multiplied by time) minus costs of the intervention. Mean net benefit was higher in the OT group with a 76% chance of being cost-effective (higher net benefit) over usual care at a median wage value of US$44.74 [US$36,88] per hour.

Two studies assessed psychoeducation targeting prevention of MDD relapse/recurrence. A Japanese study comparing family psychoeducation maintenance treatment with usual care reported significantly more relapse-free days in the maintenance treatment group. The intervention was considered cost-effective with a probability of almost 100% at a willingness-to-pay (WTP) of US$31 [US$30] per depression-free day. No cost-utility results were reported (Shimodera et al., 2012). In contrast, an individual psychoeducation prevention program (PEP) reported by Stant et al. (2009) in the Netherlands was more expensive and less effective in terms of depression-free days compared with TAU. If supplemented with psychiatric consultation or CBT, outcomes with PEP were slightly better than TAU, but neither combination was cost-effective. Follow-up duration was shorter in the Japanese study (9 months) than in the Dutch study (36 months).

Ekers et al. (2011) conducted a relatively small study (n = 47 participants) to examine the cost-effectiveness of BA delivered by non-specialist mental health nurses compared to TAU. The authors found a significant difference between groups in QALY's of 0.20 (95% CI 0.01 to 0.39; p = 0.042) in favour of BA and an incremental cost-utility ratio (ICUR) of US$ 8,301/QALY [£5,756/QALY].

Two types of short-term psychotherapy were compared in a Finnish context (PDT and SFT). No significant differences in costs or effects were observed though PDT trended towards lower costs and greater improvements. No cost/QALY was reported (Maljanen et al., 2012).

Management of MDD in elderly (55+) people identified through primary care screening was assessed by one study. Interpersonal psychotherapy did not result in significant clinical change compared to TAU over 12 months but did incur non-significantly higher total costs. Uncertainty around the cost-effectiveness estimate suggested that the intervention was unlikely to be cost-effective (Bosmans et al., 2007).

Combinations of and comparisons between psychotherapeutic interventions and pharmacotherapy

Eight trials showed conflicting results for the comparison of combination therapy (psychotherapy with pharmacotherapy) with monotherapy (either pharmacotherapy or psychotherapy alone). Domino et al. (2008) compared CBT with fluoxetine (an SSRI) and a combination of both in a sample of American adolescents with MDD. Compared to pill placebo at 12 weeks, fluoxetine alone was more cost-effective (US$ 30,582/QALY [US$23,737/QALY]) than fluoxetine with CBT (US$ 158,652/QALY [US$123,143/QALY]). Furthermore, addition of CBT to fluoxetine was not cost-effective compared with fluoxetine alone (US$ 591,121/QALY [US$ 458,818/QALY]) at 12 weeks. Results from the same trial indicated that the combination of fluoxetine plus CBT became more cost-effective than fluoxetine alone over a longer follow-up of 36 weeks (>90% probability at a threshold of US$ 128,836 [US$ 100,000]). The authors concluded combination therapy is both clinically effective and cost-effective (Domino et al., 2009).

Byford et al. (2007) studied whether CBT in addition to SSRI treatment was cost-effective in UK adolescents attending outpatient mental health clinics, who had not responded to an initial brief intervention. Compared with TAU, at 28 weeks there was no significant difference in costs or clinical outcomes though there was a trend towards higher costs and worse clinical outcomes for combination therapy. Lynch et al. (2011) studied CBT as an add-on to medication switch in young people with SSRI-resistant depression. Addition of CBT to medication switch was associated with higher costs but also higher gains in depression-free days at 24 weeks compared with medication switch alone (Incremental Cost Effectiveness Ratio - ICER of US$ 221 [US$ 188] per depression-free day or US$ 92,812/QALY [US$78,948/QALY]).

Sava et al. (2009) examined CBT, REBT and fluoxetine individually and followed patients for 6 months after completion of the intervention. The authors did not find significant differences between treatment groups in depression severity, depression- free days or QALYs. Due to

lower costs, the psychotherapeutic interventions were more cost-effective than fluoxetine at US$ 4,375/QALY [US$1,638/QALY] and US$ 4,632/QALY [US$1,734/QALY] for CBT and REBT, respectively, against US$ 6,109/QALY [US$2,287/QALY] for fluoxetine (before vs. after treatment).

Among low-income ethnic minority women with major depression in Washington, Revicki et al. (2005) compared either pharmacotherapy (paroxetine potentially followed by bupropion) or CBT with "community" referral, consisting of education about depression and its treatment along with referral to usual providers of mental health care services in the community. At 12-month follow-up, pharmacotherapy was slightly more cost-effective than CBT (US$ 39,570/QALY [US$30,023/QALY] vs. US$ 49,514 [US$ 37,568/QALY]) compared with community referral.

Direct comparison between antidepressant agents
Only one study examined differences between various antidepressant medications. Wade et al. (2008) examined the cost-effectiveness of escitalopram compared to duloxetine in treating patients with MDD. The authors found that treatment with duloxetine was associated with higher cost, higher mean sick leave and higher depression scores over the 24-week study period (Wade et al., 2008).

Severe and refractory major depressive disorder
Electroconvulsive therapy and repetitive transcranial magnetic stimulation
A small study of people with severe depressive episodes (n=46) compared repetitive transcranial magnetic stimulation (rTMS) with electroconvulsive therapy (ECT). In the six months after treatment, total costs for ECT (treatment, services and informal care) were lower than for rTMS, and ECT was more effective (Knapp et al., 2008, McLoughlin et al., 2007).

Combined CBT plus TAU
A UK study compared addition of CBT to TAU with TAU alone in primary care patients who did not respond to medication for at least 6 weeks. Over 12 months, the costs of health and social care, out-of-pocket expenses and productivity losses did not differ between groups. However, CBT incurred an additional expense of US$ 1,270 [GBP £910] per patient and resulted in improved outcomes with in ICUR of US$ 20,817/QALY [GBP £14,911/QALY] (Hollinghurst et al., 2014).

DISCUSSION

Main Results

The present systematic review presents a comprehensive overview of health economic evidence for the various treatment modalities for major depression. Several economic evaluations of clinical trials have been conducted in the area of major depression, covering pharmacotherapeutic treatments as well as different types of psychotherapeutic interventions, with some studies comparing both. Only one study evaluated the cost-effectiveness of electroconvulsive therapy and transcranial magnetic stimulation.

For moderate MDD, family psychoeducation was considered cost-effective compared to TAU (Shimodera et al. 2012). In contrast, Stant et al. (2009) found that individual psychoeducation was outperformed by TAU in clinical effectiveness and cost-effectiveness. The difference in the results of psychoeducation could be attributed to differences in treatment format (family vs. individual) or to differences in follow-up duration (9 vs. 36 months). Two studies examined CBT alone, but using different methodological approaches. Using a pre-post analysis, Sava et al. (2009) found CBT and REBT were more cost-effective than fluoxetine on account of their relative input prices. In contrast, Revicki et al. (2005) found CBT was less cost-effective than pharmacotherapy, compared with community referral. However it is clear that both study design, population and setting (Romania vs. USA) are likely to play a major role in these differences between findings.

A relatively broad literature examined the effects of monotherapy with SSRIs and CBT, or the combination of both in patients with moderate MDD. Domino et al. reported the combination of CBT with SSRIs was clinically effective and cost-effective compared to monotherapy, but only in the longer term (Domino et al., 2008; 2009). Lynch et al. (2011) showed higher clinical gains as well as higher costs in favour of combined treatment compared to monotherapy with SSRIs. Finally, Byford et al., (2007) found no significant differences between combined treatment and monotherapy in cost or clinical effectiveness. It should be noted that the interventions, although similar, had differences. In Lynch et al. (2011) trial CBT was added to medication switch, while in Byford et al. (2007) trial patients received CBT and started receiving SSRIs at the same time. Thus, results should be interpreted with caution due to limited comparability between the examined trials. Concerning direct comparison between antidepressants, one study found escitalopram dominated duloxetine (Wade et al., 2008).

Importantly, for several interventions (behavioural activation, occupational therapy, short-term psychological therapies, interpersonal psychotherapy) only results from a single study were identified (Schene et al., 2007, Bosmans et al., 2007, Maljanen et al., 2012) limiting the generalizability of conclusions. With regard to severe and refractory MDD, only two clinical studies of different interventions were identified (Hollinghurst et al., 2014, Knapp et al., 2008), and consequently no generalizations can be made.

Quality of economic evaluations

The overall methodological quality of the included economic evaluations was relatively high. The majority of studies described the methods in a transparent way, reducing possible biases related to methodology of economic outcomes assessment. However, the results of the trial-based economic evaluations rely heavily on the methodology of the randomised controlled trials. Thus, we examined the included RCTs for a spectrum of possible sources of bias related to the methodology. The results of the risk-of- bias assessment indicated that the included studies presented overall low risk of bias in most of the items examined except for blinding of personnel and participants, since this type of blinding is inherently difficult or impossible following exposure to active psychotherapeutic interventions. Therefore, the conclusions of the present systematic review should be interpreted with caution due to high risk of performance bias.

Strengths and limitations

One of the strengths of the present review is the systematic method employed to reduce the risk of bias and to provide reliable findings and conclusions. Moreover, this paper examined the validity of the included studies and presents a detailed quality appraisal. However, the work also has several limitations. A formal meta-analysis could not be conducted due to the high diversity in outcomes across the included studies. Moreover, this heterogeneity of results limited the comparability of the findings and our ability to draw robust conclusions regarding relative cost-effectiveness of interventions. Finally, it should be noted that the cost effectiveness of a particular intervention might differ substantially between countries due to variations in usual care, differences in the way new treatments are introduced, and in costs of inputs such as the salaries of health professionals between countries. Thus, the present findings should be interpreted with caution, and clinicians and policy makers should take into account any national or regional evidence in order to draw conclusions about the cost effectiveness of an intervention for major depression.

Evidence gaps and future research

Little is known about the economics of occupational therapy, short-term psychological therapies, behavioural activation, psychodynamic psychotherapy, rational emotive behavioural therapy and interpersonal psychotherapy for the treatment of moderate MDD and/or prevention of progression to more severe disease. Additionally, little empirical evidence is available on the cost-effectiveness of treatment options for severe MDD. There are gaps in knowledge regarding which medication is likely to be most cost-effective and for which patient groups, and which psychological therapy is to be preferred. There is also relatively little information on the long-term impact of treatments. No published evidence was identified regarding the cost-effectiveness of self-help programmes delivered through the Internet by therapists or healthcare workers other than qualified psychotherapists. Similar trials are ongoing in this area, such as Internet-delivered treatment for individuals with depressive symptoms (Lisanne Warmerdam, Smit, van Straten, Riper, & Cuijpers, 2010), which may provide a cost-effective approach to limiting disease progression with early intervention.

The present review, and earlier draft stages, formed part of the WHO Research Agenda for Health Economic Evaluation project, where priorities for economic research in mental health and nine other subject areas were discussed by a panel of experts (Tordrup et al. 2015). Suggested research priorities for MDD, based on the limitations of the available evidence, include: economic primary studies of rarely evaluated interventions (e.g. self-help interventions); long-term head-to-head comparisons of well studied treatments (e.g. CBT, CBT in combination with SSRIs) against usual care, using routinely available real-world data; analysis of the disease course to enable prediction of progression, thereby ensuring treatments are targeted at those unlikely to recover naturally; and elucidation of genetic components to treatment response. Importantly, when considering interventions that are supported by extensive evidence and are known to work in treating depression, the next step should be to target patients most likely to respond.

CONCLUSIONS

In conclusion, there is some economic evidence underpinning many of the interventions routinely used to treat major depressive disorder. Wide variability was observed in study outcomes, probably attributable to differences in population, interventions or follow-up periods. Significant economic evidence gaps remain in the area of major depressive disorder.

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Statement of interest
The authors have no financial conflicts of interest to declare.

Ethical standards
The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Availability of data and materials
Data supporting the present findings are publicly available. For further details, the reader is encouraged to contact the corresponding authors.

PART III

Individual Participant Data Meta-Analyses

CHAPTER 6

EFFICACY OF SELF-GUIDED INTERNET-BASED COGNITIVE BEHAVIORAL THERAPY IN THE TREATMENT OF DEPRESSIVE SYMPTOMS

A META-ANALYSIS OF INDIVIDUAL PARTICIPANT DATA

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ABSTRACT

Importance:
Self-guided internet-based cognitive behavioural therapy (iCBT) has the potential to increase access and availability of evidence-based therapy and reduce the cost of depression treatment.

Objectives:
To estimate the effect of self-guided iCBT in treating adults with depressive symptoms compared with controls and evaluate the moderating effects of treatment outcome and response.

Data sources:
A total of 13,384 abstracts were retrieved through a systematic literature search in PubMed, Embase, PsycINFO and Cochrane Library from database inception to January 1, 2016.

Study selection:
Randomized controlled trials in which self-guided iCBT was compared with a control (usual care, waiting list or attention control) in individuals with symptoms of depression.

Data extraction and synthesis:
Primary authors provided individual participant data from 3876 participants from 13 studies of 16 eligible studies. Missing data were handled using multiple imputations. Mixed-effects models with participants nested within studies were used to examine treatment outcomes and moderators.

Main outcome measures:
Outcomes included the Beck Depression Inventory, Centre for Epidemiological Studies Depression Scale and the 9-item Patient Health Questionnaire. Scales were standardized across the pool of the included studies.

Results:
Of the 3876 study participants, the mean (SD) age was 42.0(11.7) years, 2531 (66.0%) of 3832 were female, 1368 (53.1%) of 2574 completed secondary education, and 2262 (71.9%) of 3146 were employed. Self-guided iCBT was significantly more effective than controls on depressive symptoms severity (β = −0.21; Hedges g = 0.27) and treatment response (β = 0.53; odds ratio, 1.95; 95% CI, 1.52-2.50; number needed to treat, 8). Adherence to treatment was associated with lower depressive symptoms (β = −0.19; P = .001) and greater response to treatment (β = 0.90; P < .001). None of the examined participant and study-level variables moderated treatment outcomes.

Conclusions and relevance:
Self-guided iCBT is effective in treating depressive symptoms. The use of meta-analysis of individual participant data provides substantial evidence for clinical and policy decision-making, because self-guided iCBT can be considered as an evidence-based first step approach in treating symptoms of depression. Several limitations of the iCBT should be addressed before it can be disseminated into routine care.

INTRODUCTION

Many studies have found that depressive symptoms can be effectively treated with psychotherapy, pharmacotherapy or both (Cuijpers, Andersson, et al., 2011; Cuijpers et al., 2013; Karyotaki et al., 2016; Karyotaki et al., 2016). Nevertheless, many people with depressive symptoms do not seek help and even well-resourced health care systems find it difficult to marshal enough qualified therapists to offer psychological interventions. Access barriers to psychotherapy include limited availability of trained clinicians, high cost of treatment, and fear of stigmatization (Barney, Griffiths, Christensen, & Jorm, 2009; Mohr et al., 2006; Schroder et al., 2015; Titov, 2011). As a consequence, a significant number of individuals suffering from depressive symptoms remain untreated (Gavin Andrews et al., 2001; Spijker, Bijl, de Graaf, & Nolen, 2001).

Self-guided forms of internet-based cognitive behavioural therapy (iCBT) without therapist support, can allow physicians, such as general practitioners, to provide easy and affordable access to psychological treatments and reduce the cost of such treatments. A meta-analysis found a small but significant effect size of self-guided iCBT compared with control conditions (Andersson & Cuijpers, 2009). However, recent large trials found a range of effects, varying from small to moderate effect sizes (Klein et al., 2016; Björn Meyer et al., 2015) to no effect (Gilbody et al., 2015; Phillips et al., 2014). These contradicting findings drew much attention and raised concerns about the benefits of these interventions.

Randomized clinical trials (RCTs) and study-level systematic reviews often lack adequate power and precision in their estimates. Statistically underpowered samples also preclude identification of clinically useful moderators or predictors of treatment outcome (Bower et al., 2013). Meta-analyses using individual participant data (IPD) estimate aggregate effect sizes using IPD from RCTs. The IPD maximize power to detect a true effect while allowing the exploration of study variability (e.g., level of support, treatment adherence, setting, etc.) and participant characteristics as moderators of treatment outcome. The present study reports the results of an IPD meta-analysis of trials on self-guided iCBT for adult depressive symptoms compared with control conditions. The term 'self-guided iCBT' is defined as CBT delivered via the internet, which may involve automated feedback but does not provide support related to the therapeutic content.

METHODS

Eligibility Criteria

Studies were included if the participants were adults (aged > 18 years) with elevated symptoms of depression based on any diagnosis, or any self-report scale of depression. Only those RCTs in which self-guided iCBT was compared with a control condition (usual care, waiting list or attention control) were included. No language or publication status exclusions were applied.

Study Identification and Selection Process

The analysis was completed in compliance with the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) IPD Statement (Stewart et al., 2015). We used an existing database on psychological treatments for depression (Cuijpers, van Straten, Warmerdam, et al., 2008) that is updated annually by a systematic literature search in the bibliographic databases of PubMed, Embase, PsycINFO and Cochrane Library (from inception to January 1, 2016). In these searches, various index and free terms of psychotherapy and depression are used in different combinations (full search strings for PubMed are provided in Appendix A). Two researchers (PC and EK) independently examined titles and abstracts of 13,384 papers. The full text of studies that possibly met inclusion criteria according to one of the two reviewers was retrieved. In case of disagreement regarding inclusion, consensus was sought through discussion. We also asked key researchers in the field whether they knew of unpublished trials.

Data Collection and Data Items

Authors of eligible papers were contacted for permission to use their datasets. Reminders were sent after 2 weeks and, if necessary after 1 month. If no response was received, we excluded the trial. Authors were asked to provide data on socio-demographic, clinical and intervention characteristics including information regarding randomized group, baseline and follow up total scores of depressive symptoms, treatment adherence information (total number of sessions completed divided by total number of treatment sessions), age, gender, educational level (primary, secondary and tertiary education), employment status (employed or unemployed), relationship status (in a relationship or not) and comorbid anxiety symptoms at baseline (yes or no; based on a clinical interview or elevated anxiety symptoms ratings on self-report measures). Finally, we combined all individual datasets into a merged dataset, using a generic standardised protocol for integrating individual participant datasets (Appendix E3). We also used study level variables, which were available from the full reports (type of comparator condition, recruitment, level of support). The selection of moderator variables has been based on previous literature related to moderators either of face-to-face CBT or iCBT (Peter Bower et al., 2013; Hamilton & Dobson, 2002).

Risk of bias Assessment in Individual Studies

We examined the risk of bias in the included studies using the criteria of the Cochrane Collaboration 'risk of bias assessment tool (Higgins & Altman, 2008; Higgins & Green, 2008). Two independent reviewers evaluated the included studies to determine whether there was a risk for bias related to selection, performance, detection, attrition and outcome reporting. In case of unclear risk of bias for 1 or more key domains, we contacted the first authors of the included studies for clarifications.

Traditional meta-analysis

We conducted a traditional meta-analysis to examine differences among the 13 studies that provided the IPD and the 3 studies that did not. We used data reported in the articles to

calculate the effect sizes (Hedges' g) (Cohen, 1988). The reader is referred to Appendix E3 for details regarding the methods of the traditional meta-analysis.

Individual Participant Data Meta-analysis

Studies included in this IPD meta-analysis used measures such as the Centre of Epidemiologic Studies Depression Scale (Radloff, 1977), the Beck Depression Inventory – I (Beck et al., 1961) or II (Beck et al., 1996) (hereafter referrer to Beck Depression Inventory) or the 9-item Patient Health Questionnaire (Kroenke, Spitzer, & Williams, 2001) to monitor change in depressive symptoms severity. These depression measures were standardized by transformation into z-scores across the pool of the studies before conducting the main analysis.

Missing outcome data at the post-treatment assessment were estimated using multiple imputation under the missing-at-random assumption (mi impute mvn in STATA software, version 13.1; StataCorp). This method generated one hundred imputed datasets using data on baseline depressive symptoms scores, age, sex, and group. These new imputed datasets included the observed and the imputed standardized depressive symptoms scores for the missing values. They were analysed separately using the selected model and the results were averaged according to Rubin's rules (Rubin, 2004). We also conducted sensitivity analyses using only participants with complete data after treatment to examine whether there was a difference between those who dropped out of the RCTs and those who provided post-treatment data.

In a 1-stage IPD meta-analysis we merged all IPD from all studies with participants nested within studies. One-stage IPD-MA yields more precise and less biased estimates of effect, maximises the power and accounts for parameter correlation (Debray, Moons, Abo-Zaid, Koffijberg, & Riley, 2013; Stewart & Parmar, 1993). We calculated the standardised β coefficient for the examined comparisons. This estimate indicates how many SDs the dependent variable (depressive symptoms severity or the log odds ratio [OR] of treatment response) changes, per SD increase in the predictor variable. Thus, the higher the β is the greater the effect of the predictor variable on the dependent variable, while there is no association between the variables if the β is zero. All analyses were conducted with STATA statistical software, version 13.1. The primary analysis was 2-fold. First, we analysed the effects of the interventions on depressive symptoms severity at the end of the treatment using a multilevel mixed effects linear regression (using a random intercepts model with a random effect for each trial and fixed effects for the intervention and the symptoms severity, using STATA's mixed command). The post treatment depression scores were used as the dependent variable and trial arm condition (treatment vs control) as the independent variable, while controlling for baseline depressive symptoms severity

Second, we analysed the effects of the intervention on treatment response (defined as a 50:% reduction in baseline depressive symptoms scores) at the post-treatment assessment using a multilevel mixed effects logistic regression (using a random intercepts model with a random effect for each trial and fixed effects for the intervention and the depressive symptoms severity,

using STATA's melogit command). The response (yes or no) was the dependent variable, and condition was the independent variable.

Finally, we ran a 2-stage IPD meta-analysis analysing the IPD separately in each study and then combining the estimates to calculate the pooled effect sizes (Hedges's g) for depressive symptoms severity. Two-stage IPD meta-analysis facilitates analysis standardisation across the included studies and estimation of outcomes that are not available in the published reports, such as treatment response (Riley et al., 2010). Similarly, we calculated the OR of treatment response and numbers needed to treat (NNTs), which allowed us to compare the results of the present meta-analysis with those reported in earlier meta-analyses. In addition, 2-stage IPD also allowed us to examine the moderation effect of study-level variables. Thus, subgroup-moderator analyses were conducted using a mixed effects model in which the random effects model was used to pool studies within subgroups, whereas between subgroup differences were tested as fixed effects. We also ran meta-regression analyses to examine the association between treatment duration and treatment outcomes (severity of depressive symptoms and treatment response).

Exploration of Variation in Effects – Participant-level moderators.
We tested whether available demographic and clinical characteristics moderated the effect of self-guided iCBT on depression outcomes (depressive symptoms severity and treatment response). Not all included studies reported data on the examined moderators (for precise numbers regarding the missing data, see Table 1 and Table 2). To examine moderators, we added the interaction between each potential moderator and treatment outcome on depression severity into the multilevel mixed effects. We similarly added the interaction between each potential moderator and treatment response into the multilevel mixed-effect logistic regression model. Each potential moderator was included in separate model as a main effect.

Treatment Adherence as a predictor within the treatment group
We examined whether adherence to treatment predicted within treatment group effect size for the experimental condition only, using a linear mixed model, which regressed post-treatment depressive symptoms severity on treatment adherence and baseline depressive symptoms severity (fixed effects) and using random intercepts for the studies. Treatment adherence was defined as the total number of sessions that each participant completed divided by the total number of treatment sessions.

RESULTS

Study Selection and IPD Obtained
The systematic search resulted in 16 eligible articles of 1885 full-text articles screened. We were able to obtain IPD from 13 of the 16 eligible trials (81%), yielding a total of 3876 participants (Berger, Hammerli, et al., 2011; Christensen, Griffiths, & Jorm, 2004; de Graaf et al., 2009; Farrer et al., 2011; Gilbody et al., 2015; Kleiboer et al., 2015; Klein et al., 2016; B. Meyer et al.,

2009; Björn Meyer et al., 2015; Mira et al., In press; Moritz, Schilling, Hauschildt, Schroder, & Treszl, 2012; Phillips et al., 2014; Spek, Nyklíβek, et al., 2007). Three eligible datasets (Clarke et al., 2005; Clarke et al., 2009; Clarke et al., 2002) were unavailable and thus could not be included in the IPD meta-analyses. Figure 1 shows the study selection process.

Study and participant characteristics

Seven of included studies recruited participants through the community. The included RCTs examined iCBT, with interventions comprising from 5 to 11 online sessions. Four of the included trials provided support related to the technical aspects of the online platforms whereas 9 trials were purely self-guided. The control conditions used were attention placebo, no treatment, treatment as usual or waiting list. The included studies were conducted in 6 countries: Australia, Germany, Spain, Switzerland, the Netherlands, and the United Kingdom (Table a in Appendix E1 presents a summary of studies characteristics).

Of the 3876 adults with, the mean (SD) age of 42.0 (11.7) years, 2531 (66.0%) of 3832 were female, 1368 (53.1%) of 2574 completed secondary education, and 2262 (71.9%) of 3146 were employed. The mean baseline depressive symptoms scores were 25.7 on the Centre of Epidemiological Studies-Depression Scale, 28.3 on the Beck Depression Inventory and 14.1 on the 9-item Patient Health Questionnaire in their respective studies. Finally, 71 (1.8%) of 3876 randomised participants did not start the treatment or did not provide baseline and post-treatment data, and 1048 (27.0%) of 3876 dropped out of the RCT and did not provide post-treatment depressive symptoms scores (Table b. in Appendix E1 provides a summary of participants characteristics).

Risk of bias assessment

All included studies scored low on all examined items of the Cochrane risk of bias tool. Random allocation sequences were adequately generated and the allocation was sufficiently concealed in all included RCTs. Participants were not masked because this is difficult to achieve in psychotherapy research. All studies used self-report outcome. measures. Missing data were imputed as part of the present IPD to minimize study attrition bias. Finally, studies were assessed as being free of outcome reporting bias and other sources of bias (see Table c. in Appendix E1)

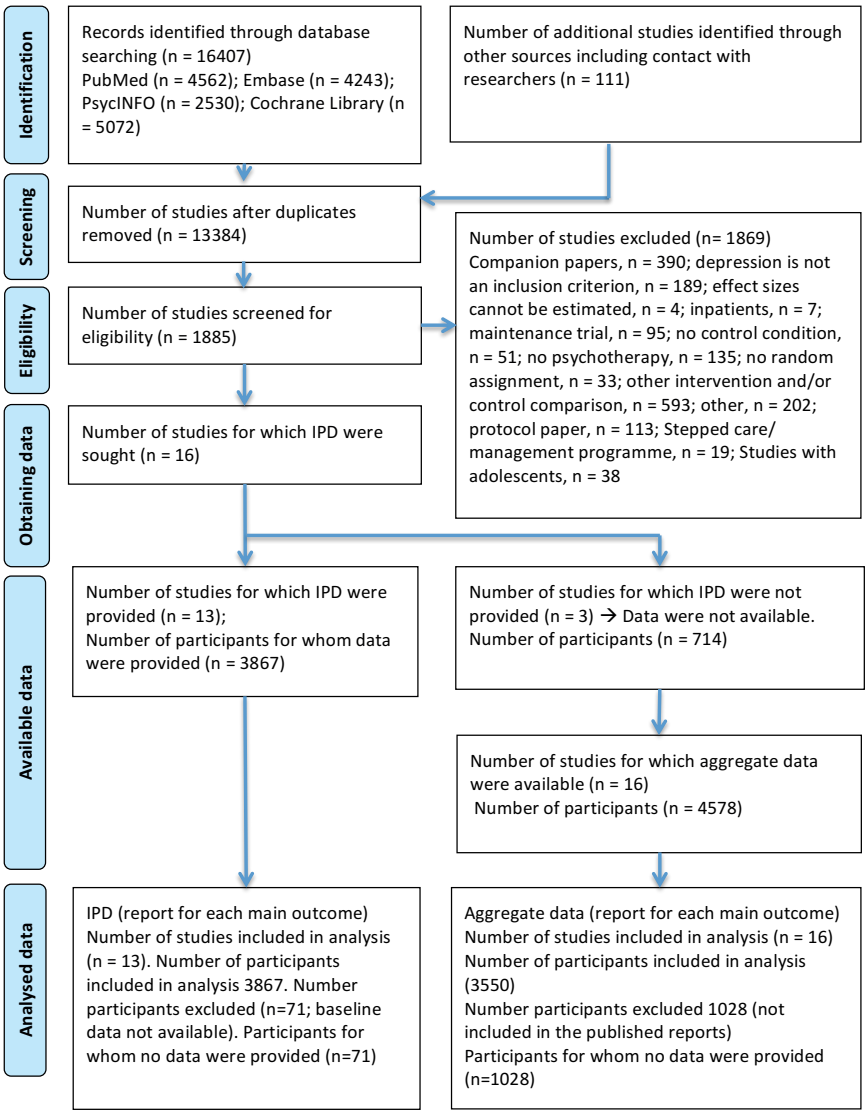

Figure 1. PRISMA IPD Diagram of studies selection process

Results of traditional Meta-analysis

Sixteen studies examined the comparison between self-guided iCBT and control groups. The results of the traditional meta-analysis revealed that self-guided iCBT outperformed the control conditions at post-treatment assessment (g = 0.33, 95% confidence interval, [CI], 0.19-0.46; P < .001). Heterogeneity was moderate to high and significant (I2 = 71%, 95% CI 51-82%; P < .001). There was no significant difference between the outcome findings of studies included in the present IPD meta-analysis and studies with unavailable data (P = .95) (Figure 2). There was

some indication of publication bias. With the use of Duval and Tweedie's Trim and Fill, method, values for five studies were imputed and the point estimate reduced to g = 0.21 (95%CI 0.07-0.34), and Egger's test was significant (P <.01) (Figure a in Appendix E2).

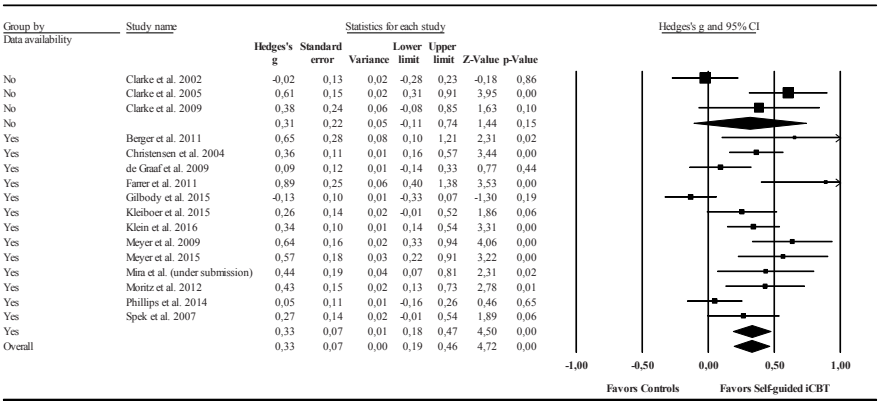

Figure 2. Forest plot of traditional meta-analysis.

One-stage IPD meta-analysis - Depressive symptoms severity

Table 1 presents the main findings of the 1-stage IPD meta-analysis on depressive symptoms severity at post-test (ranging from 6 to 16 weeks after randomization). There was a significant effect of self-guided iCBT over control conditions on depressive symptoms (β = −0.21; P < .001). Complete cases yielded similar outcomes (β = -0.19; P < .001). None of the participant-level variables (socio-demographic and clinical characteristics) significantly moderated outcome at post-treatment (Table 1). However, adherence to treatment predicted significantly better outcomes within the self-guided iCBT group (β = -0.19; P =.001).

Two-stage IPD meta-analysis – Depressive symptoms severity

The 2-stage IPD meta-analysis resulted in a pooled effect size of g = 0.27 (95% CI 0.17-0.37; P < .001) in favor of self-guided iCBT (Table d. in Appendix E1). Similar outcomes were obtained in complete cases analyses (g = 0.32, 95% CI 0.17-0.46; P < .001). None of the examined study-level variables (type of comparator condition, recruitment, level of support and treatment duration) was significantly associated with treatment outcome (see Table d., Figure b., Figure c. in Appendix E1 & E2).

One-stage IPD meta-analysis - Treatment Response

A significant effect in favour of self-guided iCBT over controls was found for treatment response (β = 0.53; P < .001; Table 2). Complete cases analyses resulted in similar outcomes (β = 0.50; P < .001). None of the socio-demographic and clinical characteristics of participants were significantly associated with treatment response (Table 2). Treatment adherence significantly predicted treatment response (β = 0.90; P < .001).

Table 1. Mixed effects models outcomes on depressive symptoms severity, 1-stage IPD [a]

	Full sample			Complete cases analysis [b]		
	Nobs (Nst)	Parameter (SE)	P Value	Nobs (Nst)	Parameter (SE)	P Value
Variable						
Main effects – depression severity						
Baseline severity	3795	0.57 (0.02)	< .001	2818	0.57 (0.02)	<.001
Treatment group	(13)	-0.21 (0.03)	< .001	(13)	-0.19 (0.03)	<.001
Age						
Baseline severity	3786	0.58 (0.02)	< .001	2809	0.57 (0.02)	
Treatment group	(13)	-0.32 (0.10)	< .001	(13)	-0.33 (0.11)	<.01
Age * Treatment group		0.003(0.002)	0.28		0.003(0.002)	.19
Gender						
Baseline severity	3788	0.58 (0.02)	< .001	2811	0.57 (0.02)	<.001
Treatment group	(13)	-0.22 (0.03)	< .001	(13)	-.0.22 (0.04)	<.001
Gender * Treatment group		0.05 (0.06)	.45		0.07 (0.06)	.26
Educational level						
Baseline severity	2538	0.58 (.024)	< .001	1973	0.57 (0.02)	<.001
Treatment group	(10)	-.031 (.011)	< .001	(10)	-0.31 (0.12)	0.00
Educational level * Treatment group						
Secondary vs. primary education		0.15 (0.13)	.21		0.19 (0.13)	.14
Tertiary vs. primary education		0.03 (0.13)	.79		0.02 (0.13)	.84
Relationship status						
Baseline severity	3568	0.57 (0.02)	< .001	2630	0.56 (0.02)	<.001
Treatment group	(12)	-0.20 (0.05)	< .001	(12)	-0.18 (0.05)	<.001
Relationship status * Treatment group		0.006 (0.06)	.91		-0.004 (0.06)	.95
Employment status						
Baseline severity	3067	0.55 (0.02)	< .001	2194	0.53 (0.02)	<.001
Treatment group	(10)	-0.27 (0.06)	< .001	(10)	-0.26 (0.07)	<.001
Employment status * Treatment group		0.12 (0.08)	.11		0.14 (0.08)	.07
Comorbid anxiety						
Baseline severity	1728	0.62 (0.03)	< .001	1447	0.62 (0.03)	<.001
Treatment group	(9)	-0.20 (0.05)	< .001	(9)	-0.19 (0.05)	<.001
Comorbid anxiety * Treatment group		-0.10 (.07)	.17		-0.11 (0.07)	.13
Baseline severity of depression						
Baseline severity	3795	0.59 (0.02)	< .001	2818	0.59 (0.02)	<.001
Treatment group	(13)	-0.20 (0.03)	< .001	(13)	-0.19 (0.03)	<.001
Baseline severity * Treatment group		-0.03 (0.03)	.22		-0.04 (0.03)	.17

Nobs: Number of observations; Nst: Number of studies; SE: Standard error

[a] Parameters are standardized beta weights of the composite z-scores of CESD, BDI and PHQ-9. Two tailed *P* values are presented

[b] This a sensitivity analysis that was conducted including only participants who completed post-treatment depression questionnaires

Table 2. Outcomes on treatment response, 1-stage IPD[a]

	Full sample			Complete cases analysis[b]		
	Nobs (Nst)	Parameter (SE)	P Value	Nobs (Nst)	Parameter (SE)	P Value
Variable						
Main effects – treatment response						
Treatment group	3795 (13)	0.53 (0.09)	< .001	2818 (13)	0.50 (0.09)	<.001
Age						
Treatment group	3786	0.70 (0.32)	< .01	2809	0.70 (0.33)	<.01
Age*Treatment group	(13)	-.004 (0.007)	.60	(13)	-0.005 (0.007)	.53
Gender						
Treatment group	3788	0.56 (0.09)	< .001	2811	0.54 (0.11)	<.001
Gender*Treatment group	(13)	-0.07 (0.18)	.68	(13)	-0.09 (0.18)	.61
Educational level						
Treatment group	2538	0.83 (0.36)	< .01	1973	0.77 (0.38)	<.01
Educational level*Treatment group	(10)			(10)		
Secondary vs. primary education		-0.40 (0.38)	.31		-0.37 (0.41)	.36
Tertiary vs. primary education		-0.16 (0.40)	.68		-0.07 (0.42)	.85
Relationship status						
Treatment group	3568	0.56 (0.14)	< .001	2630	0.56 (0.14)	<.001
Relationship status*Treatment group	(12)	-0.07 (0.18)	.71	(12)	-0.10 (0.18)	.58
Employment status						
Treatment group	3067	0.72 (0.18)	< .001	2194	0.72 (0.20)	<.001
Employment status*Treatment group	(10)	-0.34 (0.21)	.12	(10)	-0.40 (0.22)	.07
Variable						
Comorbid anxiety						
Treatment group	1728	0.61 (0.16)	< .001	1447	0.63 (0.17)	<.001
Comorbid anxiety*Treatment group	(9)	0.23 (0.26)	.38	(9)	0.27 (0.27)	.32
Baseline severity of depression						
Treatment group	3795	0.53 (0.09)	< .001	2818	0.50 (0.09)	<.001
Baseline severity*Treatment group	(13)	0.03 (0.08)	.41	(13)	-0.023 (0.09)	.80

Nobs: Number of observations; Nst: Number of studies; SE: Standard error

[a] Parameters are standardized beta weights of treatment response. Two tailed *P* values are presented

[b] This is a sensitivity analysis that was conducted including only participants who completed post-treatment depression questionnaires

Two-stage IPD meta-analysis - Treatment Response

The OR was 1.95 (95% CI 1.52-2.50; P < .001) in favor of the self-guided iCBT group, which corresponds to a NNT of 8 (95% CI 6-12). Similar outcomes were found when we conducted complete cases analysis (OR = 1.88 95% CI 1.34-2.64; P < .001; NNT =9; 95% CI 6-17). None of the examined study-level variables was significantly associated with treatment response (see Table e., Figure d. and Figure e. in Appendix E1 & E2).

DISCUSSION

In this study we examined the effects of self-guided iCBT on severity and treatment response. We aimed to identify moderators of treatment outcome. We found that self-guided iCBT had lower depressive symptoms severity and greater treatment response compared with control conditions at post-test. These findings were robust in complete cases analyses. Treatment adherence was significantly related to treatment outcomes within the self-guided iCBT group. None of the examined participant and study-level variables significantly moderated the treatment effect.

The finding that self-guided iCBT results in a significant effect on depression outcomes is consistent with previous literature (Richards & Richardson, 2012). However, the present IPD meta-analysis provides stronger evidence and improves the precision of the estimates due to the novel methodological approach used. Moreover, previous literature did not examine numbers needed to treat. The current findings indicate that we need to treat 8 individuals with depressive symptoms with self-guided iCBT to expect a 50% symptom reduction. Although this NNT is relatively large and its clinical relevance could be doubted, it can still have a considerable impact when large groups of patients use the treatment, especially considering the low costs of self-guided iCBT.

The role of treatment adherence in outcomes has been identified by a previous review in the field conducted by Donkin and colleagues (Liesje Donkin et al., 2011). The authors concluded that the number of sessions correlated with outcomes in the interventions that targeted at depressive symptoms (Liesje Donkin et al., 2011). In other words, participants did better when they adhered to the intervention. However, treatment adherence follows the course of the intervention and may be influenced by response to treatment as much as vice versa. As previous research findings have suggested, there are may be different pre-existing factors (e.g. age, gender, etc.) that influence the association between treatment adherence and treatment outcomes (Karyotaki et al., 2015).

It is also interesting that baseline depressive symptoms scores did not moderate treatment outcomes. This contrasts with the findings from the IPD meta-analysis of low intensity interventions by Bower et al. (2013), who found that higher levels of depressive symptoms at baseline were associated with better depressive outcomes (greater decrease in depressive symptoms) after the completion of low intensity interventions. However, this effect was relatively small. The authors concluded that it might not be clinically relevant and that it is safer to assume that low intensity interventions work equally across a range of severities.

Strengths and Limitations

Among the strengths of the present study was its high power to detect small statistically significant differences between intervention and controls and to yield more precise and robust evidence compared with traditional meta-analyses. Moreover, the included RCTs had high

methodological quality, which allows us to be confident that the present analysis is relatively free from critical biases. However, many internet-delivered interventions incorporate repeated use of symptom inventories with each online session. This repeated administration of symptom inventories might yield lower mean scores with each wave of measurement (completer biases related to self-report ratings) (Jorm, 2009). Moreover, the included studies did not report on recruitment issues related to large-scale, fully unguided internet-administered interventions, including factors such as repeated registration attempts by individuals who did not meet inclusion criteria or who were dissatisfied with their intervention allocation. These matters constitute a potential threat to validity and should be addressed by future research in this field.

Several limitations of our IPD meta-analysis should be mentioned. We observed moderate to high heterogeneity. Unfortunately, the subgroup analyses did not provide any indication of which study-level variables are associated with the observed heterogeneity. Moreover, our findings are at risk (albeit low) of availability bias because we could not access data from 3 eligible studies of the 16. However, the results of the traditional meta-analysis indicated that the findings of these 3 unavailable trials did not differ from the findings of the included RCTs. Another limitation is that we could not examine duration of symptoms as a potential moderator of treatment outcome. Duration of symptoms is important because individuals with chronic depressive symptoms may not always respond rapidly to treatment. Furthermore, most of the included trials recruited their self-referred participants through the community thereby limiting our ability to generalize the present results to clinical samples. Finally, there was some indication of publication bias, suggesting that unpublished trials with negative findings might be missing from the present sample of studies.

CONCLUSIONS

Self-guided iCBT produces results that are encouraging. The absence of a significant difference in treatment outcomes associated with clinical and socio-demographic characteristics implies that self-guided iCBT can be used by most individuals with depressive symptoms regardless of the severity of their symptoms or their socio-demographic background. Currently, antidepressant medications are widely used in the treatment of depressive symptoms, whereas psychotherapeutic interventions are provided to a lesser degree, despite many individuals with depressive symptoms preferring psychotherapy to antidepressants (van Schaik et al., 2004). However, the high treatment costs and the limited number of trained clinicians hamper the implementation of psychotherapy in practice.

The findings of the present IPD meta-analysis suggest that self-guided iCBT may be a viable alternative to current first step treatment approaches for symptoms of depression, particularly in those individuals who are not willing to have any therapeutic contact. This form of intervention seems to be valuable for patients with primary depressive problems and those with depressive symptoms in the context of a primary somatic problem (Fischer et al., 2015; Schröder et al., 2014). This self-help form of CBT can provide treatment access at low cost to large numbers of

individuals worldwide who have depressive symptoms. Although it is beyond the scope of this study, unguided iCBT has several limitations that should be addressed before it is disseminated as part of routine care (e.g., the high dropout rates, small effects compared with face-to-face and guided Internet interventions, and possible participants selection bias).

Given the effects found for treatment adherence, future research should focus on improving retention of participants in self-guided iCBT programs with the aim of maximizing positive therapeutic outcomes. Further research is also needed to examine additional moderators (e.g., sleep quality, cognitive performance, duration of symptoms, etc.), long-term outcomes and the value of adding therapist or coach support to these treatments. Finally, future studies should focus on the pragmatic effectiveness of iCBT in routine care settings

Author Contributions
Ms Karyotaki had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design
Karyotaki, Kleiboer, Mira, Botella Arbona, Bretón-López, Gilbody, Moritz, Cuijpers.

Acquisition, analysis, or interpretation of data
Karyotaki, Riper, Twisk, Hoogendoorn, Kleiboer, Mackinnon, Meyer, Littlewood, Andersson, Christensen, Klein, Schröder, Scheider, Griffiths, Farrer, Huibers, Phillips, Gilbody, Moritz, Berger, Pop, Spek, Cuijpers.

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Critical revision of the manuscript for important intellectual content
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Obtained funding
Riper, Scheider, Gilbody, Cuijpers. Administrative, technical, or material support: Mira, Botella Arbona, Littlewood, Andersson, Christensen, Klein, Schröder, Bretón-López, Farrer, Gilbody, Moritz, Spek, Cuijpers.

Study supervision
Riper, Kleiboer, Moritz, Cuijpers.

Conflict of Interest Disclosures
Dr. Klein reported having received funding for clinical trials (German Federal Ministry of Health, Servier), payments for presentations on Internet interventions (Servier), payments for workshops and books (Beltz, Elsevier and Hogrefe) on psychotherapy for chronic depression and on psychiatric emergencies. No other disclosures were reported.

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Role of the Funder/Sponsor
The European Commission had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The decision to submit the article for publication was a condition of the funding and was made before any results were available.

Additional Contributions
We would like to thank Dr. Carmen Domnica Cotet for help with data extraction. Dr. Carmen Domnica Cotet did not receive additional compensation in association with her work on this article.

CHAPTER 7

INTERNET-BASED SELF-HELP INTERVENTIONS FOR DEPRESSION IN ROUTINE CARE-REPLY

Karyotaki, E., Riper, H.,
& Cuijpers, P. (2017).

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IN REPLY TO:

Ebert, D., & Baumeister, H. (2017). Internet-based self-help interventions for depression in routine care. JAMA Psychiatry, 74(8), 852-853.

We thank David Daniel Ebert and Harald Baumeister for their insightful response. We agree that the results of our study should be considered with caution, as we also indicated in our paper (Karyotaki et al., 2017)

The authors highlight that they would have appreciated a more detailed discussion about the interpretation of the clinical significance of our findings, especially regarding the small effect. While we acknowledge that we need to be cautious when interpreting the clinical relevance, we consider self-guided interventions, that have a NNT of 8, to be potentially helpful for populations that are not willing to seek professional help, for use during watchful waiting in primary care, or for example in low- and middle-income countries with no or only a limited infrastructure for mental health services1. We would like here to note that as reported by Muñoz and colleagues 'Massive open online interventions have the potential to increase the reach, scalability, and affordability of psychological interventions (Muñoz et al., 2015). Even a small effect can have a huge impact when it is applied in large populations. Therefore, self-guided iCBT can have a large impact on mental health, despite the small effect sizes. We would also point to the fact that an effect size of g=0.27 may be small, but not so very different from other treatments. For example, the effect size of antidepressant medication versus placebo is also only g=0.31 (95% CI 0.27 – 0.35) (Turner et al., 2008).

Second, Ebert and Baumeister refer to potential publication bias. We agree that this may be a problem, but we examined this in our study and found that the effect size was only affected to a small extent after adjustment for publication bias. Similarly, with regard to control conditions, our sample was not restricted to waiting list, and we did not find significant differences between types of controls.

Third, clinical samples may indeed differ from individuals in the community. However, unguided interventions are typically conducted outside the clinical field in people recruited from the community. Therefore, the results of our study are probably valid in the populations for which the interventions are meant. Furthermore, we performed moderator analysis of recruitment location (Table d. and Table e. in Appendix E1) and found no significant differences.

We do agree on the problem of heterogeneity in our results. That was also one of the main focuses of our study. Heterogeneity could not be fully explained by the examined moderators. As we suggested in the discussion, future research should address additional moderators, such as sleep quality, cognitive performance and duration of symptoms (Karyotaki et al., 2017).

Finally, the authors would have appreciated a discussion on the role of guidance and the higher effectiveness of guided interventions. There is indeed evidence suggesting that guided interventions present higher effects and adherence rates compared to self-guided interventions (Richards & Richardson, 2012). However, self-guided interventions do not need a professional taskforce to deliver interventions and is much cheaper and easy to implement, compared to guided interventions. Furthermore, the number of studies directly comparing guided with self-guided interventions are scarce, and the evidence that guided interventions are more effective is not conclusive (Baumeister, Reichler, Munzinger, & Lin, 2014).

CHAPTER 8

PREDICTORS OF TREATMENT DROPOUT IN SELF-GUIDED WEB-BASED INTERVENTIONS FOR DEPRESSION: AN "INDIVIDUAL PATIENT DATA" META-ANALYSIS

Karyotaki, E., Kleiboer, A., Smit, F., Turner, D. T., Pastor, A., Andersson, Berger, T., Botella,c..,Breton, J. M., Carlbring, P.Christensen, H., de Graaf,E. Griffiths, K., Donker, T., Farrer, L.,. Huibers1, M. J. H, Lenndin, J., Mackinnon, A., Meyer, B., Moritz, S., Riper, H., Spek, V., Vernmark,K., Cuijpers, P.(2015).

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ABSTRACT

Background:
It is well known that web-based interventions can be effective treatments for depression. However, dropout rates in web-based interventions are typically high, especially in self-guided web-based interventions. Rigorous empirical evidence regarding factors influencing dropout in self-guided web-based interventions is lacking due to small study sample sizes. In this paper we examined predictors of dropout in an individual patient data (IPD) meta-analysis to gain a better understanding of who may benefit from these interventions.

Method:
A comprehensive literature search for all Randomized Controlled Trials (RCTs) of psychotherapy for adults with depression from 2006 to January 2013 was conducted. Then we approached authors to collect the primary data of the selected studies. Predictors of dropout, such as socio-demographic, clinical, and intervention characteristics were examined.

Results:
Data from 2,705 participants across ten RCTs of self-guided web-based interventions for depression were analysed. The multivariate analysis indicated that male gender (RR=1.08), lower educational level (primary education; RR=1.26) and comorbid anxiety symptoms (RR= 1.18) significantly increased the risk of dropping out, while for every additional four years of age, the risk of dropping out significantly decreased (RR=.94).

Conclusions:
Dropout can be predicted by several variables and is not randomly distributed. This knowledge may inform tailoring of online self-help interventions to prevent dropout in identified groups at risk.

INTRODUCTION

A large body of research has suggested that web-based interventions can be effective treatments for depression with comparable effect sizes to face-to-face treatment (Andrews, Cuijpers, Craske, McEvoy, & Titov, 2010; Cuijpers, Donker, van Straten, Li, & Andersson, 2010; Spek, Cuijpers, et al., 2007). Self-guided forms of web-based treatment (i.e. interventions that patients work through on their own with no guidance) do not rely on having therapists available. These interventions can be made available to a greater number of people at very low incremental cost, thus increasing access and availability. They also maintain anonymity and overcome concern about stigmatization making them more acceptable to many people.

However, meta-analytic studies have also shown that self-guided web-based interventions (i.e. interventions that patients work through on their own without guidance) show less promising results than guided web-based interventions that are delivered with support from a coach or therapist (Andersson & Cuijpers, 2009; Cuijpers, Donker, et al., 2011; Gellatly et al., 2007; Richards & Richardson, 2012; Spek, Cuijpers, et al., 2007). One explanation for the difference in effectiveness between guided and unguided web-based interventions is that the human support involved in guided interventions increases treatment adherence through accountability to a coach or therapist who is seen as trustworthy, benevolent, and an expert (Mohr, Cuijpers, & Lehman, 2011). Furthermore, guided web-based interventions often not only involve a supportive coach who helps participants through the program but also more often than unguided interventions include human contact before treatment [e.g. during a diagnostic interview; (Johansson & Andersson, 2012)] or include referral by a therapist (Berger, Caspar, et al., 2011; Marks & Cavanagh, 2009), which may add to feelings of accountability.

In line with the idea of 'supportive accountability', higher dropout rates have been found in unguided web-based interventions for depression compared to guided web-based interventions with average levels of adherence estimated at 26% in unguided interventions and 72% in guided interventions (Richards & Richardson, 2012). In addition, empirical evidence has shown that greater exposure to the intervention is related to better treatment outcomes (Donkin et al., 2011) suggesting that efforts to increase adherence rates in web-based interventions may lead to better outcomes. To gain a better understanding of who may benefit from unguided web-based interventions and how we can improve adherence rates, there is a strong need to identify characteristics of individuals and interventions that are related to treatment dropout, as unguided interventions are much easier to implement and less costly than guided web-based interventions.

A few studies have already investigated this issue (Christensen, Griffiths, & Farrer, 2009; Waller & Gilbody, 2009). However, studies that have been conducted so far often lack the power to find reliable effects of predictors and moderators. In the current study we bring together the data from separate studies and employ a new strategy named Individual Patient Data (IPD) meta-analysis. IPD meta-analysis was developed to address research questions that require

large sample sizes and is based on data pooled from individual RCTs (Bower et al., 2013). In this way it increases the power and precision to detect predictors and moderators. This study aimed to identify socio-demographic, clinical, and intervention characteristics that predict dropout rates in self-guided web-based interventions for depression. In the context of the present paper, the term adherence is defined as the percentage of treatment modules that were completed. Dropout rate was defined as a completion rate of less than seventy five per cent of the intervention modules, as we considered that in most interventions the core treatment elements are administered in this part of the treatment.

METHOD

Search Strategy for identification and selection of studies

We used an existing database of randomized trials of psychological treatments for depression. The database has already been used by several published meta-analyses (www.evidencebasedpsychotherapies.org) and its detailed description can be found elsewhere (Cuijpers, van Straten, Warmerdam, & Andersson, 2008). This database has been developed and is periodically updated by a comprehensive literature search of the following health related databases: Cochrane Central Register of control trials, PubMed, Psych Info and Embase from 1996 to January 2013. In these electronic searches, various key terms covering the concepts of psychotherapy and depression were used in different combinations (both MeSH-terms and text words). For a detailed description of the searches the reader is referred to Cuijpers et al. (2008). In addition, several systematic reviews and meta-analyses in this research field have been crosschecked throughout the development of this database in order to ensure that no trials were missing. Along with the use of this database, we contacted authors and asked them to provide us with access to the datasets of trials that were not yet published.

Inclusion Criteria for studies

We included (a) randomized controlled trials (RCTs), (b) comparing a psychological intervention (c) delivered through the web (d) without any form of personal guidance, (e) with a control or comparison group, (f) aimed at adults with depression (based on a clinical interview or on elevated depressive symptoms ratings on self-report measures).

Quality Assessment

The validity of the studies included in the present IPD meta-analysis was examined by two independent reviewers (E.K. and D.T.) according to four criteria of the Cochrane Risk of Bias assessment tool (Higgins et al., 2011; Higgins & Green, 2011). We tested if the allocation concealment was adequately generated (sequence generation), the allocation was sufficiently concealed (allocation concealment), the knowledge of the allocated intervention was adequately prevented (blinding), and any incomplete outcome data were sufficiently addressed. However, we did not consider that incomplete outcome data could influence the results of the present IPD meta-analysis since the primary aim of this paper was to identify factors influencing treatment dropout. Finally, when the information that was provided in the papers did not provide sufficient

details to assess quality, we contacted the primary authors to ask what procedure was actually followed and subsequently we ran sensitivity analysis based on what the papers reported. Disagreement between the reviewers was resolved through discussion, and if needed a third reviewer was consulted (P.C.).

Data extraction and preparation

Two authors independently extracted data included in the present meta-analysis (E.K. and D.T.). We first contacted authors of RCTs that satisfied the inclusion criteria and we asked them whether they would permit us access to their primary datasets. We identified the variables, which were common to all or most of the included datasets. These were the following: randomized group (therapy or control), baseline and follow up depression scores, age, gender, educational level, employment status, relationship status (being in or not in a relationship), number of modules completed and presence of anxiety symptoms at baseline (yes/no; based on a clinical interview or on elevated anxiety symptoms ratings on self-report measures). Finally, we combined the individual datasets into one large pooled dataset.

Statistical analysis

In this paper, data were extracted only for intervention groups and not for control comparison conditions as we only looked at predictors of treatment adherence. Studies included in the present IPD meta-analysis used measures such as the CES-D or the BDI to monitor change in depression. These depression measures were standardized (transformed into z-scores) across the pool of the studies. We also conducted sensitivity analyses to assess the impact of baseline severity on dropout from treatment for CES-D and BDI separately. We analysed the effects of predictors on dropout from treatment using a design-based analysis of the data to account for the clustering of participants within studies. Individual patient data were analysed by a poisson regression model for patients nested within studies to obtain relative risks (RR) of treatment dropout on the selected factors, adjusted for the other predictors in the Poisson model and taking into account the clustered data structure by obtaining robust (Hubert-White) standard errors based on the first-order Taylor-series linearization method as implemented in Stata version SE 12.1 (StataCorp., 2011). This methodological approach is computationally efficient in synthesizing and estimating the effect of predictors (Zou, 2004). We conducted the analysis in three steps. First we conducted a series of bivariate analyses to assess the RR of each factor at a time (the so called 'bivariate model'). Then we repeated the analyses with all factors simultaneously entered in the Poisson model (the so called 'complete model'). Lastly, we simplified the complete model by only retaining those factors in the model that were statistically significant by eliminating factors that were not significant (the 'parsimonious model'). Finally, we performed sensitivity analysis to assess the impact of the included studies' quality on dropout from treatment and we checked whether the assumption of linearity was met for the relationship between dependent and independent variables.

RESULTS

Selection of included studies

A total number of 14,164 abstracts were identified through bibliographic database searching. After the removal of duplicates, 10,474 abstracts were examined. A total of 1,476 full text papers were retrieved for potential inclusion. After the exclusion of 1,123 studies, 353 trials were included in the database. We searched through this database and in additional sources (grey literature, researchers on this field) and we identified 13 eligible RCTs for inclusion in the current meta-analysis. We were unable to retrieve the data from three studies (Clarke et al., 2005; Clarke et al., 2009; Clarke et al., 2002) and included 10 RCTs in the present IPD meta-analysis (77%). Figure 1 presents the study selection process. Overall, the three studies that we did not include (n=302) were very similar to the 10 included studies, except for the method of recruitment (all participants in these 3 studies were recruited through an HMO in the United States, while none of the other studies recruited patients this way). The main outcome measures in these studies were the CES-D and the Patient Health Questionnaire-8 items (PHQ-8) (Clarke et al., 2005; Clarke et al., 2009; Clarke et al., 2002).

Study Characteristics

In the present IPD meta-analysis, ten studies with a total of 2,705 participants were included. All the examined studies recruited their participants from the community, and they were conducted across six different countries: Australia (n=2), Germany (n=2), Spain (n=1), Sweden (n=1), Switzerland (n=1), and the Netherlands (n=3). The majority of the included studies used self-report outcome measures for depression on which the participants needed to score above a predetermined cut-off point in order to be included in the trial. Seven out of the ten included studies used the BDI as a primary outcome measure while the remaining trials used the CES-D.

All included unguided web-based interventions were based on three different theoretical models of psychotherapy. The majority of the included studies used interventions based on CBT principles (n=8). The remaining studies used either PST (n=1) or they compared web-based CBT with IPT (n=1). Table 1 shows selected characteristics of the included studies.

Most of the participants were female (n=1,945/2,705; 72%) and most were educated at University level (n=1,933/2,705; 71%). The modal age group into which participants fell was 25-34 years (n=741/2,705; 27%). The average score on the CES-D at baseline assessment was 35.5 (SD= 11.5), while the average score on the BDI was 28.4 (SD=13.5) indicating a high degree of severity. The average score on the CES-D and the BDI reduced at the post-treatment assessment to 24.2 (SD=13.2; n=650) and 20.7 (SD=14.8; n=495) respectively. The majority of the sample reported symptoms of comorbid anxiety (n=1,689/2,705; 71.6%) (Table 2).

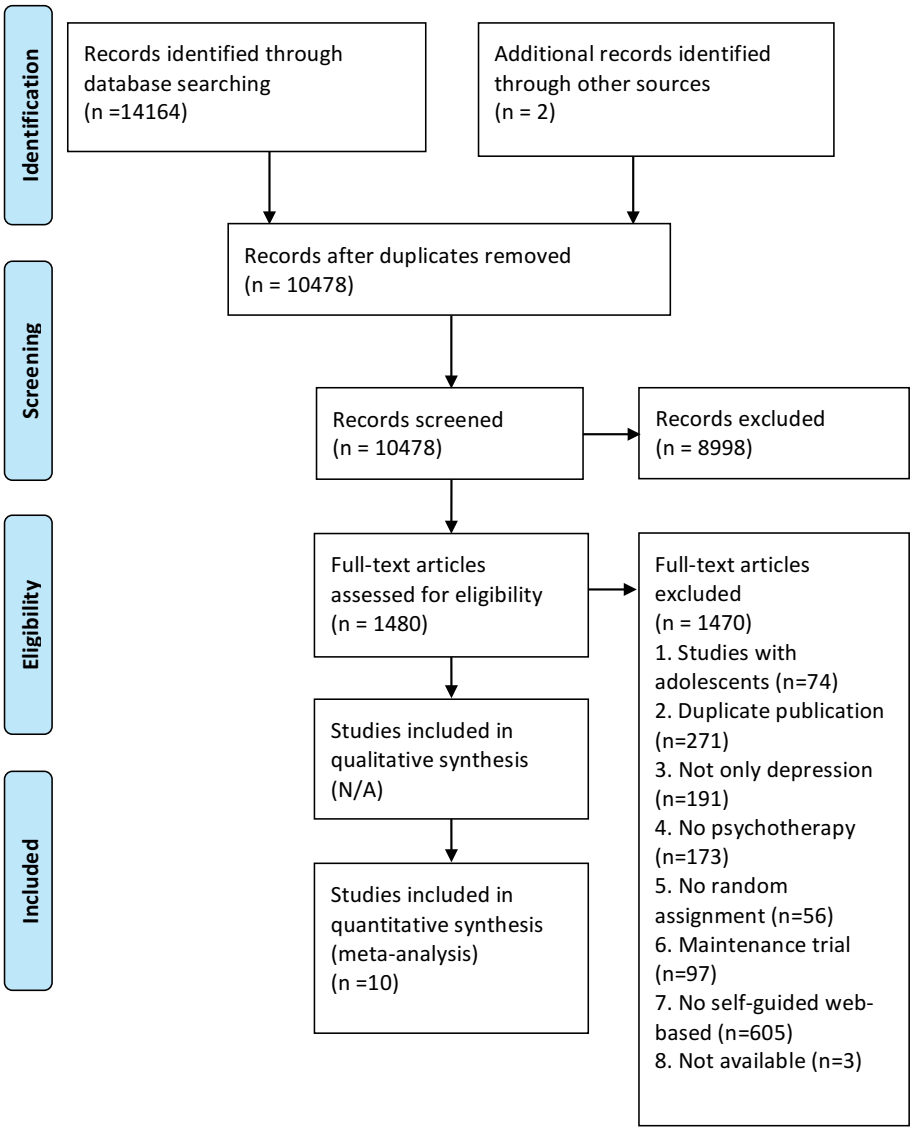

Figure 1. PRISMA flow chart of study selection process

Across the 10 included RCTs, 1,090 participants (40%) dropped out before the completion of 25% treatment modules, 1,604 (59%) dropped out before completing half of the treatment modules. Further, levels of dropout increased to 70% (1,880/2,705) when we looked at the number of participants that completed 75% of treatment modules. Finally, only a small percentage of 17% (452/2,705) completed all treatment modules.

Table 1. Characteristics of included studies

Study	Inclusion Criteria	N	Outcome Measure	Average n. of modules completed/Total n. of Modules	Intervention	Quality Ass.*	Country
Berger, Caspar, et al. (2011)	BDI-II>13, MDD (Mini-DIPS)	25	BDI-II	7/10	CBT	+ + + +	Switzerland
Botella et al. (under submission)	18–65 years old. BDI-II not>28	36	BDI-II	7/8	CBT	+ + + +	Spain
De Graaf et al. (2009; de Graaf et al., 2011)	8-65 years old, BDI score≥16	100	BDI-II	3/8	CBT	+ + + +	The Netherlands
T. Donker et al. (2013)	CES-D≥27	1864	CES-D	1/4 (CBT); 2/4 (IPT)	CBT, IPT	+ + + +	Australia
Farrer et al. (2011)	K10>20	38	CES-D	2/5	CBT	+ + + +	Australia
Kleiboer et al. (under submission)	35>CES-D>16; 15>HADS>8	107	CES-D	2/5	PST	+ + + +	The Netherlands
B. Meyer et al. (2009)	Depression (BDI)	320	BDI	4/10	CBT	+ + + +	Germany
Moritz, Schilling, Hauschildt, Schroder, and Treszl (2012)	18-65 years old, depression (BDI)	105	BDI	6/10	CBT	+ + + +	Germany
Spek et al (2008; 2007)	50-57 years old, EDS>12	102	BDI-II	5/10	CBT	+ + + +	The Netherlands
Vernmark, Lenndin, Bjarehed, et al. (2010)	MDD (SCID-I-CV)	24	BDI	7/8	CBT	+ + + +	Sweden

BDI: Beck Depression Inventory; CBT: Cognitive and Behavioural Therapy; CES-D: Centre of Epidemiological Studies for Depression Scale; EDS: The Endiburg Depression Scale; HADS: Hospital Anxiety and Depression Scale; IPT: Interpersonal Psychotherapy; K10: The Kessler psychological distress scale; MDD: Major Depressive Disorder; Mini DIPS: Mini Diagnostic Interview for Psychiatric Disorders; n: number; Quality Ass. : Quality Assessment; SCID-I-CV: Structural Clinical Interview for DSM-IV axis I disorders; PST: Problem Solving Therapy

* A positive or a negative sign is given in this column for the following quality criteria respectively: allocation sequence, allocation concealment, blinding of assessors, and incomplete outcome data (whether or not the study used intention-to-treat analysis)

Table 2. Demographic and clinical characteristics of the included sample

Characteristics	
Age, 25-34 years old n (%)	741/2705 (27)
Gender, females' n (%)	1945/2705 (72)
CES-D at the baseline, mean (SD)	35.5 (11.5)
BDI at the baseline, mean (SD)	28.4 (13.5)
CES-D at post-treatment, mean (SD)	24.2 (13.2)
BDI at post-treatment, mean (SD)	20.7 (14.8)
Comorbid Anxiety, n (%)	1689/2705 (71.6)

BDI: Beck Depression Inventory; CES-D: Centre of Epidemiological studies for depression scale; n: number of patients; SD: Standard Deviation

Quality Assessment

All the included studies had acceptable methodological quality. The sequence was adequately generated, and the allocation was adequately concealed. Moreover, all trials used self-report outcome measures, which were administered via the Internet. Therefore, blinding of assessors was considered as adequately addressed across the ten studies of this IPD meta-analysis. However, the participants were not blinded to the interventions, and this may have caused bias. Finally, all included RCTs used intention-to-treat (ITT) analyses including all the randomized participants in their post treatment analyses, which indicates that incomplete outcome data were adequately addressed (see Table 1).

Predictors of dropout in self-guided web-based treatment for depression

The results of the bivariate analyses indicated that male gender (RR=1.05; 95% CI: 1.01 ~ 1.11), participants with a low educational background (primary education; RR= 1.23; 95% CI: 1.13 ~ 1.33), the presence of comorbid anxiety symptoms (RR=1.18; 95% CI: 1.01 ~ 1.38) and CBT-based interventions (RR= 1.19; 95% CI: 1.03 ~ 1.39) were related to a higher risk of dropping out. Finally, the chance of dropping out significantly decreased for every four years of age increase (RR=.98; 95% CI: .97 ~ 99). The remaining variables/potential predictors (baseline severity of depression, relationship status, number of intervention modules and employment status) failed to achieve a statistically significant level of $p<.05$ in the bivariate analysis (see table 3).

Additionally, under the parsimonious model, male gender (RR=1.08; 95% CI: 1.03 ~ 1.13), lower educational level (primary education; RR=1.26, 95% CI: 1.14 ~ 1.39), older age (RR=.94; 95% CI: .87 ~ 1.02) and comorbid anxiety (RR= 1.18; 95%CI: 1.01 ~ 1.38) remained statistically significant predictors of dropout from treatment. However, in our sample, CBT/not-CBT intervention status was confounded with number of modules. Thus, the effects of intervention type could not be disentangled from the number of modules and we excluded these predictors from the parsimonious model. Finally, depression severity, employment status and relationship status remained non-significant after controlling for the other predictors (see table 3).

Table 3 Predictors to self-guided web-based psychotherapy for depression

			Bivariate Analyses			Multivariate Model Nobs=411			Parsimonious Model Nobs=2355		
Predictors	Nst	Nobs	RR	95%CI	p	RR	95%CI	p	RR	95%CI	p
Gender (male)	10	2702	1.05	1.01~1.11	.04	1.04	.82~1.31	.72	1.08	1.03~1.13	.002
Age (continious per 4y increse)	10	2700	.98	.97~.99	.001	1,01	.96~1.07	.05	.98	.97~.99	.004
Education											
Low vs. high	10	2695	1.23	1.13~1.33	.000	1.64	1.11~2.43	.01	1.26	1.14~1.39	.000
Middle vs. high	10	2695	.98	.88~1.10	.85	1.19	.97~1.48	.09	.94	..87~1.02	.08
Being in a relationship (yes/no)	8	751	1.09	.95~1.25	.20	1.08	.82~1.43	.05	-	-	-
Employed (yes/no)	8	748	.97	.79~1.20	.82	1.08	.97~1.48	.05	-	-	-
Baseline severity of depression	10	2690	1.05	.99~1.11	.07	1.24	.98~1.57	.06	-	-	-
Comorbid anxiety	9	2358	.09	1.01~1.38	.02	1.36	1.01~1.82	.04	1.18	1.01~1.38	.03
Type of intervention (CBT vs. others)	10	2705	1.19	1.03~1.39	.001	.7	.53~1.02	.07	-	-	-
N of modules (n<5)	10	2705	.88	.72~1.08	.24	-	-	-	-	-	-

CBT vs. other: Cognitive Behavioural Therapy compared to other types of psychotherapy; CI: Confidence Intervals; comp.: compare; N of modules: number of modules; Nobs: number of observations; Nst: number of studies; p: p-value; RR: Risk Ratio; Substandard Error; y: years;

Sensitivity analysis

We analysed the impact of depression severity on dropout for CES-D and BDI scores separately. Individuals who scored higher on CES-D at baseline had a slightly higher risk of dropping out than those with lower scores (RR=1.004, 95% CI 1.003 to 1.005, obs=1987 p<0.001). 'However, the increase in risk quite small and is therefore unlikely to have clinical relevance. Further, separate analysis for BDI scores at baseline did not produce statistically significant results (p>0.05). It is important to stress that the results of BDI analysis were based on a considerably smaller, though sufficiently powered, number of participants (n=718).

Three studies did not report all relevant information regarding allocation concealment in the published papers (although personal contact with the primary authors illustrated that the allocation was adequately concealed) and thus, we decided to run sensitivity analysis based on what the papers reported. We examined the impact of quality of the included studies on treatment dropout. Study quality did not significantly predict treatment dropout (p>.05). Further,

we controlled for study quality in our final parsimonious model. The predictors remained the same after adjusting for the quality of the included studies.

DISCUSSION

Main findings

The present IPD meta-analysis aimed to identify predictors of treatment dropout in self-guided web-based interventions for depression. We tested the relationship between dropout and several socio-demographic, clinical and intervention characteristics. The multivariate analysis of 2,705 individual patients' data revealed that being male; having attained a lower educational level (primary education); a younger age and having comorbid anxiety symptoms significantly increased the risk of dropping out before the completion of 75% of treatment modules and thus were related to high treatment's dropout.

Placing our findings in the wider context of the literature

The finding that gender predicted treatment dropout has not been identified by previous literature on self-guided web-based interventions. However, this result may reflect a different coping strategy between the two genders. Previous research has shown that females generally present with a higher effort to cope with depression compared to males (Babwah et al., 2006). These efforts might enhance their willingness to continue and complete web-based interventions without any form of guidance. There is also evidence to support the idea that women are generally more conscientious regarding health issues compared to men (Babwah et al., 2006). These differences in health attitudes could partly account for the differences in treatment compliance rates between the genders (Waller & S Gilbody, 2009).

A lower educational background has also been identified as a risk for dropping out in previous research and it has been suggested that low educational status is a barrier to adherence to web-based CBT because of greater difficulties in understanding the intervention content and procedure and limited abilities in using information technology which may result in diminished motivation to continue and complete a self-guided web-based treatment (Waller and Gilbody, 2009).

Unlike the results from this study that showed that younger age was related to low treatment adherence, previous research showed that younger individuals had higher adherence to web-based treatment (Christensen, Griffiths, & Farrer, 2009).

Comorbid anxiety symptoms increased the risk of dropping out of the treatment 16 per cent. It is important, however, to stress that studies included in this meta-analysis were not designed for the treatment of anxiety or to deal with comorbid anxiety and therefore the reason for this finding is unclear. Further research is needed to clarify this.

None of the remaining variables significantly predicted treatment attrition and results derived by the present IPD meta-analysis were not influenced by quality of the included studies. The lack of a significant effect on adherence of relationship status is consistent with results reported by Christensen et al. (2009). Further, Christensen et al. (2009) concluded that dropout increases with the severity of baseline depression. The findings from the present study suggest that the severity of depression does not significantly predict dropout from treatment. However, when we examined the impact of baseline severity separately for CES-D and BDI we found a significant but small higher risk for dropping out of treatment for patients who scored higher on CES-D at baseline, a result which is consistent with the conclusions of Christensen et al. (2009).

Strengths and limitations

One of the strengths of the present IPD meta-analysis was that it was based on a novel methodological approach that it is considered a gold standard for identifying predictors, moderators and mediators to treatment dropout and outcome. Combining raw individual data from several studies into one single dataset provides adequate power and precision to detect predictors of treatment attrition. Further, the systematic literature search employed by the present IPD meta-analysis reduced the risk of introducing study selection bias into the results.

In spite of the aforementioned strengths it should be noted that the present study has several limitations. Among these limitations was the risk of availability bias. We could access ten RCTs' individual patient datasets out of thirteen eligible studies. Although this is higher than in other IPD meta-analyses (Riley, Simmonds, & Look, 2007), the ten available RCTs might differ in several ways from the three unavailable studies. Moreover, some of the predictor variables were not reported across all the ten RCTs. This might have resulted in lower power to predict effects for some of the variables of interest, although the IPD was better powered to detect a true effect than a single trial. However, such small effects would be less relevant from a clinical or public health perspective.

Moreover, the participants of the present IPD meta-analysis differ from patients in clinical samples. For instance, all the participants were recruited through the community and were proactively seeking help for their symptoms. Thus, the present findings might not be generalized to the whole population with depression but it is representative for help seeking individuals in the community. It should also be borne in mind that four of the included studies conducted a diagnostic interview before inclusion of the participants (Berger, Hämmerli, Gubser, Andersson, & Caspar, 2011; de Graaf et al., 2009a; Vernmark, Lenndin, Bjärehed, et al., 2010). This may have enhanced treatment adherence by increasing any feeling of accountability. However, we considered that these studies should be retained in our analyses since they did not provide any guidance throughout treatment. Finally, in the available data intervention type (CBT vs. others) is confounded with the number of sessions and thus, it is not possible to reliably attribute dropout to a particular type of intervention or to the number of treatment modules.

All these predictors should be taken into account in future development of self-guided interventions for depression. For example, different features of web-based interventions may be appealing to different individuals and it is important to find out what works best for whom. Future interventions could, for example, employ more audio-visual components such as videos or gaming and less written material for individuals with a lower education. This knowledge will help in utilizing the self-guided form of web-based interventions in the most efficient and effective way. Future studies may need to be tailored to the particular needs of individuals with comorbid anxiety symptoms, male gender, with a low educational background and young age. Further, future research should also examine dropout at different time points or as a function of exposure to particular types of content, as treatment dropout at different time intervals may represent different processes. Other psychological predictors such as personality styles, motivation and preferences should be included in future trials to inform tailoring. This might prevent dropout in future versions of self-guided web based interventions.

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Conflict of interest
None

Ethical standards
The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

CHAPTER 9

IS SELF-GUIDED INTERNET-BASED COGNITIVE BEHAVIOURAL THERAPY (ICBT) HARMFUL? AN INDIVIDUAL PARTICIPANT DATA META-ANALYSIS

Karyotaki, E., Kemmeren, L., Riper, H., Twisk, J., Hoogendoorn, A., Kleiboer, A., Mira, A., Mackinnon, A., Meyer, B., Botella, C., Littlewood, E., Andersson, G., Christensen, H., Klein, J.P., Schröder, J., Bretón-López, J., Griffiths, K., Farrer, L., Huibers, J.H.M., Phillips, R., Gilbody, S., Berger, T., Pop, V., Spek, V., Cuijpers, P.. (2017).

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ABSTRACT

Background:
Little is known about potential harmful effects as a consequence of self-guided iCBT, such as symptom deterioration rates. Thus, safety concerns remain and hamper the implementation of self-guided iCBT into clinical practice. We aimed to conduct an individual participant data (IPD) meta-analysis to determine the prevalence of clinically significant deterioration (symptom worsening) in adults with depressive symptoms who received self-guided iCBT compared to control conditions. Several socio-demographic, clinical and study-level variables were tested as potential moderators of deterioration.

Methods:
RCTs that reported results of self-guided iCBT compared to control conditions in adults with symptoms of depression were selected. Mixed effects models with participants nested within studies were used to examine possible clinically significant deterioration rates.

Results:
Thirteen out of sixteen eligible trials were included in the present IPD meta-analysis. Of the 3806 participants analysed, 7.2% showed clinically significant deterioration. Participants in self-guided iCBT were less more likely to deteriorate (OR = 0.62, $p < .001$) compared to control conditions. None of the examined participant- and study-level moderators were significantly associated with deterioration rates.

Conclusions:
Self-guided iCBT has a lower rate of negative outcomes on symptoms than control conditions and could be a first step treatment approach for adult depression as well as an alternative to watchful waiting in general practice.

INTRODUCTION

Depression is a common and major health issue that is associated with a considerable personal and societal burden (Lepine & Briley, 2011; M. Reddy, 2010). Self-guided forms of Internet-based Cognitive Behaviour Therapy (iCBT) can increase accessibility and reduce the costs of depression treatment (Hedman, Ljótsson, & Lindefors, 2012; Muñoz et al., 2015). Over the past decade, free or commercially provided self-guided iCBT programmes have been made available to individuals with depression (Kaltenthaler et al., 2006). However, there is an ongoing discussion about the advantages and disadvantages of such programmes (Andersson & Titov, 2014). Many health care systems remain hesitant to implement self-guided iCBT. Among the barriers to implementation are concerns regarding safety and effectiveness (Waller & Gilbody, 2009). Offered as first stage treatment, self-guided iCBT has been criticised as potentially delaying individuals suffering from depression receiving effective clinical services (Robinson, Patrick, Eng, & Gustafson, 1998; Ybarra & Eaton, 2005).

Our recent individual participant data (IPD) meta-analysis demonstrated that self-guided iCBT produces encouraging effects although average effects are small in magnitude (Karyotaki et al., 2017). Small effects can be clinically useful and relevant, for instance in countries where mental health care services are scarce or inaccessible for other reasons (Karyotaki et al., 2017; Muñoz et al., 2015). Despite the ample evidence regarding the overall benefits of iCBT, possible effects harmful to individuals have been infrequently monitored. As with any other potentially effective treatment, iCBT could also result in undesirable outcomes or fail to arrest substantial ongoing deterioration(Dimidjian & Hollon, 2010). The issue of negative effects is crucial for clinical decision-making, yet limited systematic examination of this issue exists for iCBT.

In contrast to the vast majority of pharmacological trials, which rigorously measure and report adverse outcomes, only half of psychotherapeutic trials report undesirable outcomes, in particular substantial symptom deterioration (Jonsson, Alaie, Parling, & Arnberg; Vaughan, Goldstein, Alikakos, Cohen, & Serby, 2014). Previous research has shown that some forms of psychotherapy can be hazardous for some patients e.g., prolonged imaginal exposure may result in worsening of symptoms in some patients with posttraumatic stress disorder(Foa et al., 2005). With regard to self-guided psychological treatment, it has been argued that it may not be appropriate for all individuals (Newman, 2000). For instance, self-guided interventions may not be intensive enough for individuals with severe symptoms (Mohr et al., 1990). Moreover, lack of therapeutic support may jeopardize therapy outcomes as the progress of patients is not monitored (Newman et al., 2003). Most self-guided interventions are not tailored to the current depressive status of the individual and, accordingly, do not respond to symptom deterioration (Andersson & Titov, 2014).

To our knowledge symptom deterioration has not been examined in self-guided iCBT to date. It is therefore clearly important to determine the prevalence and extent of symptom deterioration in self-guided iCBT. Furthermore, given that not everyone receiving self-guided iCBT experiences

worsening of symptoms, research examining for whom this particular form of therapy may be harmful is sorely needed: individuals likely to deteriorate could be diverted to other more appropriate treatment options. However, study-level meta-analyses and randomized controlled trials (RCTs) cannot thoroughly examine moderators of deterioration due to inadequate power (Bower et al., 2013). Novel methodological approaches, such as IPD meta-analysis, are needed to identify who may experience adverse effects from self-guided iCBT. IPD meta-analysis allows us to move beyond the 'grand mean' to explore change at the individual level as well as to examine study variability (e.g. level of adherence, settings, etc.)

The present IPD meta-analysis examined rates of clinically significant symptom deterioration under self-guided iCBT compared to control conditions in adults with depression. In addition, we examined several socio-demographic and clinical variables as potential moderators of symptom deterioration. In the context of the present paper, the term 'self-guided iCBT' is defined as CBT treatment delivered via the Internet without any professional support related to the therapeutic content. The present analysis focuses on the prevalence of deterioration (numbers of persons affected) in contrast to our previous IPD meta-analysis of the present dataset in which we focused on population average outcomes due to self-guided iCBT on depression severity (Karyotaki et al., 2017)

METHODS

Studies selection process

We included individual participant data from randomised controlled trials comparing self-guided iCBT to a control condition (waiting list, treatment as usual, attention placebo or other non-active controls) for adults (^{3} 18 years old) with symptoms of depression based either on a diagnostic interview or validated self-report scales. We excluded studies that did not primarily target depression. No limits were applied for language and publication status.

To identify eligible studies, we used an existing database of trials focusing on psychological therapies for adults with depression(Cuijpers, van Straten, Warmerdam, et al., 2008). This database was developed in 2006 and is updated annually by a systematic literature search in four major bibliographic databases (PubMed, Embase, PsycINFO and Cochrane Library). The database was updated up to January 1st 2016 for the current search. In this search, various index and free terms of psychotherapy were used in combination with index and free terms of depression. Appendix A. presents the full electronic search string for PubMed. Two reviewers (PC and EK) examined 13,384 titles and abstracts independently. All full texts of papers that possibly met inclusion criteria according to one of the two reviewers were retrieved and checked for eligibility. Disagreement on the inclusion was solved through discussion. Additionally, references of recently published meta-analyses on this field were examined to ensure the inclusion of all eligible published trials. Finally, key researchers who are actively involved in this field were contacted to ask whether they were aware of unpublished trials on this topic or trials missed through the searches.

Data collection process and data items

We contacted the first or the senior author of the RCTs to request access to their datasets. In the case of no response, a reminder email was sent after two weeks and after one month. If no response was received one month after the first email, the study was excluded as unavailable. Authors provided individual participant data including socio-demographic variables (age, gender, educational level, employment status and relationship status), pre- and post-treatment depression scores, anxiety scores at baseline and the number of iCBT modules completed by each participant. All individual participant data were merged into one dataset. We also extracted study level variables available from the published reports of the included RCTs (type of control condition, recruitment method and level of support provided).

Risk of bias assessment

Two independent reviewers (EK and PC) assessed the risk of bias in the included studies according to the Cochrane risk of bias assessment tool(Higgins & Altman, 2008; JPT Higgins & Green, 2011). We examined whether the included studies were at low or high risk of selection, performance, detection, attrition, reporting and other sources of bias. In cases of uncertainty, clarification was sought from the authors of the RCT.

Measures

The included studies used either the Beck Depression Inventory [BDI-I (Beck et al., 1961) or BDI-II (Beck et al., 1996)], the Centre for Epidemiological Studies Depression Scale [CES-D (Radloff, 1977)], or the Patient Health Questionnaire [PHQ-9 (Kroenke et al., 2001)] as outcome measures of depression severity.

We classified 'clinically significant deterioration' according to each participant's reliable change index (RCI) (Jacobson & Truax, 1991), which is the most commonly used method for calculating clinically significant negative effects. This method aims to ensure that each individual's deterioration could not attributable to measurement error (Lambert, Bergin, Bergin, & Garfield, 1993) and thus might warrant clinical intervention in the context of an unsupervised intervention such as iCBT. An RCI of ±1.96 indicates that the difference in scores is likely to be due to a real change in symptoms of an individual (95% confidence level). Participants showing a clinically significant change with an increase in their score (clinically significant negative change of more than -1.96) were classified as clinically significant deteriorated(Jacobson & Truax, 1991). A reliable change index was calculated separately for each of the studies, using their pre-treatment standard deviation, and the test-retest reliability coefficient of the outcome measure (BDI = 0.93, CES-D = 0.87, PHQ-9 = 0.84).

Finally, in a sensitivity analysis we calculated 'any deterioration' as any increase of equal or more than one point on depressive symptom scales (increase ^{3} 1 BDI or CES-D or PHQ-9 point) from pre- to post-treatment. Any deterioration includes all deterioration rates (clinically significant or not).

Missing data

Missing outcome data at the post-treatment were multiply imputed. We generated one hundred imputed datasets based on the missing-at-random assumption ('mi impute mvn' in Stata version 13.1; StataCorp LP). These datasets, which consisted of the observed and the imputed deterioration rates, were analysed separately using the selected model and the results were combined using Rubin's rules(Rubin, 2004). We ran sensitivity analyses including only observed values to ensure the robustness of the results ('the complete case analysis').

Analysis

One-stage IPD

We performed a one-stage IPD meta-analysis in which the individual participant data from all included studies were merged, with participants nested within studies. A one-stage IPD approach is preferred over a two-stage approach because it allows for a more exact likelihood specification(Burke, Ensor, & Riley, 2016; Debray et al., 2013; Stewart & Parmar, 1993). We used the statistical software Stata (version 14.2) for conducting all analyses. A multilevel-mixed effects logistic regression was used to analyse the effect of the iCBT intervention on clinically significant deterioration and any deterioration. We used a random intercepts model with a random effect for each trial and fixed effect for condition (intervention vs control) using the *'melogit'* command in Stata. The binary variables *'clinically significant deterioration'* and *'any deterioration'* were used as fixed effect.

To explore the variation in outcomes between participants, we examined dichotomous and continuous baseline characteristics of the participants as potential moderators of clinically significant deterioration and of any deterioration. Moderation was tested by adding the interaction between each moderator and deterioration rates to the multilevel mixed effects logistic regression model. Similarly, we examined whether adherence (defined as number of modules completed divided by the total number of treatment modules) predicted lower deterioration rates within the intervention group.

Two-stage IPD

In addition to the one-stage IPD, we performed a two-stage IPD to examine the effects of study-level variables. We calculated the odds ratio (OR) of deterioration for each study and we pooled the outcomes using a random effects model, chosen because considerable heterogeneity across studies was expected. The OR shows the probability that an event (deterioration) will occur in the intervention group (self-guided iCBT) compared to the probability that the same event occurring in the control group. An OR of more than 1 indicates increased probability that an event will occur in the intervention group while and an OR less than 1 shows increased probability that an event will occur in the control group(Deeks et al., 2008).

To examine heterogeneity, the I^2-statistic was calculated. This is an indicator of heterogeneity expressed as a percentage: an I^2 value of 0% is interpreted as no heterogeneity, 25% as low, 50% as moderate, and 75% as high heterogeneity(Cohen, 1988). We calculated the 95%

confidence intervals (CI) around I^2 using the non-central chi-squared-based approach within the heterogeneity module for Stata(Evangelou et al., 2007; Nicola Orsini et al., 2006). Publication bias was examined by visually inspecting funnel plots and by using the Duval and Tweedie's trim and fill method, which yields an estimate of the effect size after adjusting for publication bias (Duval & Tweedie, 2000; Egger et al., 1997). We also conducted the Egger's test of the intercept to quantify the bias captured by the funnel plot and test whether it was significant[30].

Finally, we examined study-level moderators by conducting subgroup analyses using the mixed effects models in which studies were treated as random effects and subgroups were tested as fixed effects.

Sample representativeness

In our previous analysis (Eirini Karyotaki et al., 2017) we tested differences between thirteen studies that provided individual participant data and three eligible studies that did not. Results indicated that there are no statistically significant differences in depression severity outcomes between the included and the unavailable trials (Karyotaki et al., 2017). This suggests that the present sample of studies is representative. However, we could not test differences between included and unavailable trials in the current analysis since deterioration rates are not reported by the published reports of the unavailable trials.

RESULTS

Study Selection

The systematic literature search resulted in sixteen eligible studies for inclusion. The flow chart of the study selection process is presented in Figure 1. Data were available from thirteen trials including 3876 participants (Berger, Hammerli, et al., 2011; Christensen et al., 2004; Esther de Graaf et al., 2009; Farrer et al., 2011; Gilbody et al., 2015; Kleiboer et al., 2015; Klein et al., 2016; Meyer et al., 2009; Meyer et al., 2015; Mira et al., In press; Moritz et al., 2012; Phillips et al., 2014; Spek, Nyklíβek, et al., 2007). Three eligible datasets were excluded from the present IPD meta-analysis as data were unavailable (Clarke et al., 2005; Clarke et al., 2009; Clarke et al., 2002).

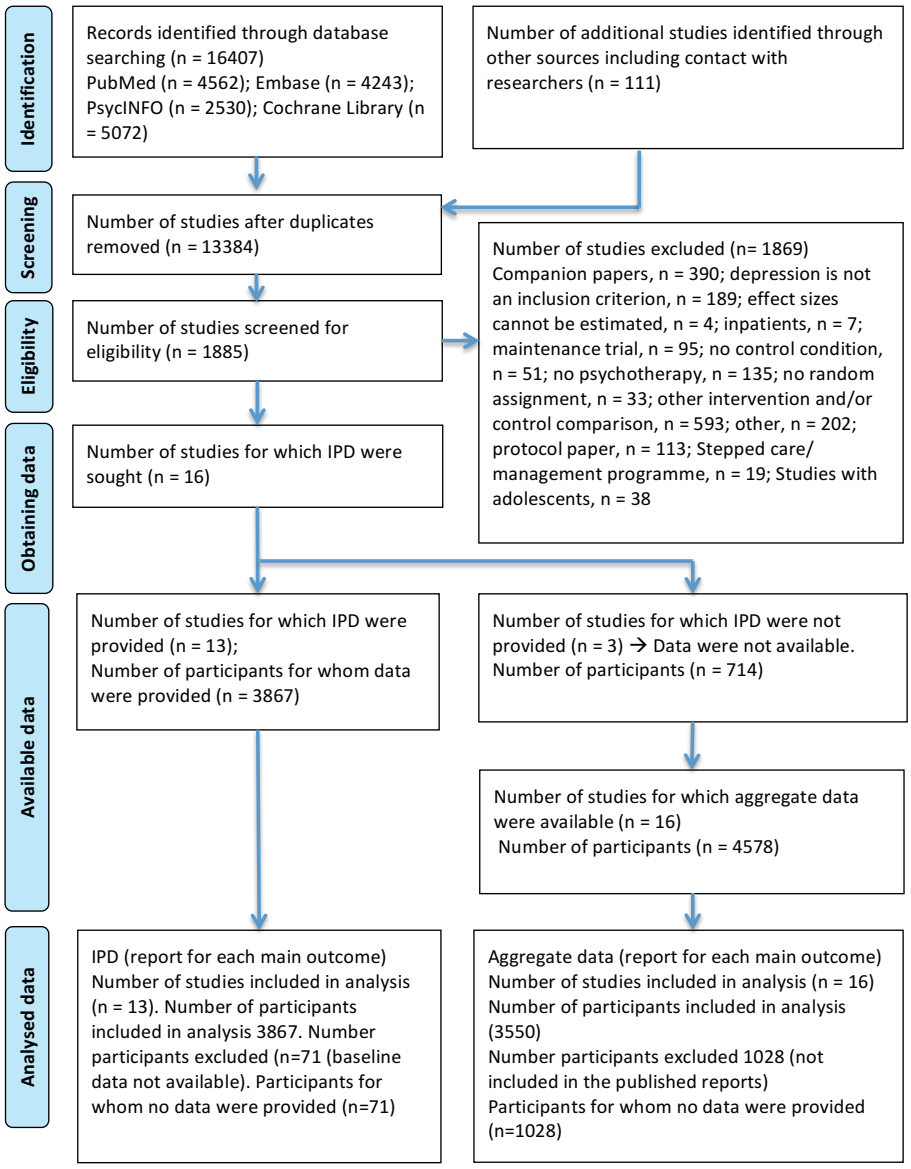

Figure 1. PRISMA IPD Diagram of studies selection process

Studies and participants characteristics

Studies characteristics are presented in Table 1. Across the thirteen included RCTs participants were recruited mainly within communities. The studies were conducted in six countries (Australia, Germany, Spain, Switzerland, the Netherlands and the United Kingdom). The included RCTs examined the effects of self-guided iCBT over control conditions (attention placebo, no

treatment, treatment as usual or waiting list). The interventions consisted of five to eleven online self-guided modules. The majority of the trials provided fully self-guided iCBT while four studies provided technical support related to technical aspects of the web-platform.

Patient characteristics of the intervention and control groups are presented in Table 2. There were no significant between-group differences in gender, age, relationship status, employment, education level, comorbid anxiety or pre-treatment scores on depression measures. Two thirds of the participants were female (n = 2531/3832, 66%), and the mean age was 42 years (SD = 11.7). Most of the participants were employed (n = 2233/3146, 71%) and had a high school degree or further education (n = 2314/2574, 90%). Participants had mean baseline scores of BDI-II = 28.3 (SD = 14.4), CES-D = 25.7 (SD = 10.8) and PHQ-9 = 14.2 (SD = 5.4). A small number of individual cases (n = 71) did not start the treatment or did not have baseline data, leaving a total of n = 3805. Finally, 1048 participants dropped out from the included RCTs and did not provide post-treatment scores of depressive symptoms.

Assessment of risk of bias

The overall risk of bias was low across the included RCTs. Random sequence was adequately generated and allocation was concealed in all included studies. Blinding of participants and personnel is not possible in psychotherapy research due to the nature of the treatment. The included RCTs used self-report outcome measure, thus blinding of outcome assessment is not applicable. As an attempt to minimise attrition bias, we multiply imputed the missing data in the present IPD. Finally, there was no indication of selective reporting and other sources of bias. For a justification of risk of bias assessment for each study, the reader is referred to our previous publication (Karyotaki et al., 2017).

Prevalence of clinically significant deterioration

Overall, 7.2% (276/3806) of participants met criteria for clinically significant deterioration, while 30.1% (1143/3806) showed deterioration of any size. Divided by treatment group, 5.8% of participants who followed self-guided iCBT and 9.1% of participants in control groups showed clinically significant deterioration. Similarly, 26.2% of participants in self-guided iCBT and 35.3% of participants in control groups experienced any deterioration. Complete case analysis showed that 6.1% and 9.1% of participants showed clinically significant deterioration in self-guided iCBT and control groups respectively. Any deterioration rates were 26.5% for self-guided iCBT and 36.6% for the control groups.

Table 1. Characteristics of included studies

Study (year)	Inclusion criteria	Outcome measure	Intervention programme	N of modules	N. iCBT	Tech. support	Control	N. Control	PT assess. (in weeks)	Country
Berger et al. (2011)	BDI-II > 13; MDD or dysthymia DSM-IV (Mini-DIPS)	BDI-II	Deprexis	11	25	No	WL	26	10	CH, DE
Christensen et al. (2004)	K10 ≥ 22	CES-D	Moodgym	5	182	No	AP	178	6	AU
De Graaf et al. (2009)	BDI-II ≥ 16;	BDI-II	Colour Your Life	9	200	No	TAU	100	8	NL
Farrer et al. (2011)	K10 ≥ 22	CES-D	MoodGYM	5	83	Yes	NT	35	6	AU
Gilbody et al. (2015)	PHQ-9 ≥ 10	PHQ-9	MoodGYM Beating the Blues;	8 5	452	Yes	TAU	239	16	UK
Kleiboer et al. (2015)	39 ≥ CES-D ≥ 16; 15 > HADS ≥ 8	CES-D	Alles Onder Controle	5	107	No	WL	106	6	NL
Klein et al. (2016)[a]	5 ≥ PHQ-9 ≥ 14	PHQ-9	Deprexis	11	192	Yes	TAU	187	12	DE
Meyer et al. (2009)	Completed at least half of the baseline BDI	BDI	Deprexis	11	320	No	WL	76	9	DE
Meyer et al. (2015)	PHQ-9 ≥ 15	PHQ-9	Deprexis	11	78	No	TAU	85	12	DE
Mira et al. (2013)	BDI-II < 28;	BDI-II	Smiling is Fun	8	80	Yes	WL	44	12	ES
Moritz et al. (2012)	Minimal to severe depression: BDI > 0	BDI	Deprexis	11	105	No	WL	105	8	DE
Phillips et al. (2014)	PHQ-9 ≥ 2 on five of the nine items, including ≥ 2 on item 1 or item 2.	PHQ-9	MoodGYM	5	318	No	AP	319	6	UK
Spek et al. (2007b)	EDS ≥ 12;	BDI-II	Colour Your Life	10	67	No	WL	58	10	NL

AP, Attention Placebo; BDI, Beck Depression Inventory; CBT, Cognitive Behavioural Therapy; CES-D, Centre of Epidemiological Studies for Depression Scale; EDS, Edinburgh Depression Scale; HADS, Hospital Anxiety and Depression Scale; IPT, Interpersonal Psychotherapy; K10, Kessler 10 Psychological Distress Scale; MDD: Major depressive disorder; Mini DIPS, Mini Diagnostic Interview for Psychiatric Disorders; *n*, number; NT, no treatment; PHQ-9, Patient Health Questionnaire; PST, Problem Solving Therapy; PT assess.: Post-treatment assessment; TAU, treatment as usual; WL: waiting list; WHO CIDI, World Health Organization Composite International Diagnostic Interview

[*] Deteriorated: reliable deterioration calculated with RCI

[a] Klein et al. 2016 trial provided therapeutic support to participants with moderate depression (PHQ-9 > 9). Participants with mild depressive symptoms received no support throughout the trial. Klein et al. 2016 stratified participants based on depression severity during randomization. Therefore, we decided to exclude all participants who received therapeutic support (PHQ-9 > 9; n = 634) from the present IPD meta-analysis.

Table 2. Patient characteristics

Total n of participants (n = 3847)		Intervention group (n = 2244)	Control group (n = 1603)
Gender female, n (%)		1507/2244 (67.4)	1024/1603 (64.2)
Age in years (mean ± sd)		41.37 ± 12.27	42.49 ± 11.99
In a relationship, n (%)		1239/2124 (58.3)	881/1489 (59.2)
Employed , n (%)		1306/1862 (70.1)	927/1255 (73.9)
Education level , n (%)	Low	154/1593 (9.7)	106/981 (10.8)
	Middle	869/1593 (54.6)	499/981 (50.9)
	High	570/1593 (35.8)	376/981 (38.3)
Pre-treatment depression scores (mean ± SD)	BDI-II	27.60 ± 13.5	29.67 ± 15.9
	CES-D	26.21 ± 10.8	25.25 ± 10.9
	PHQ-9	14.44 ± 5.4	13.8 ± 5.6
Post-treatment depression scores (mean ± SD)	BDI-II	20.36 ± 14.4	25.97 ± 16.7
	CES-D	18.6 ± 11.2	22.04 ± 12.2
	PHQ-9	9.19 ± 6.0	9.63 ± 5.9
Comorbid anxiety disorder, n (%)		425/972 (43.7)	336/789 (42.6)

One-stage IPD – deterioration rates

The outcomes of one-stage IPD meta-analysis on deterioration rates are summarised in Table 3. Self-guided iCBT resulted in significantly lower clinically significant deterioration (OR = 0.62; 95% CI 0.46 to 0.83, p < .001) compared to controls at post-treatment assessment (6 to 16 weeks post-randomisation). Sensitivity analysis on any deterioration rates and complete case analyses yielded similar outcomes, suggesting that these findings are robust. No significant associations were found between participant characteristics (age, gender, educational level, relationship status, employment status, comorbid anxiety and baseline severity of depression) or for deterioration rates in both full sample and complete case analyses. Finally, treatment adherence was not significantly associated with clinically significant (β = -0.01; SE = .37, p = 0.97) or any deterioration (β = -0.10; SE = .19, p = 0.59) within the intervention group.

Two-stage IPD – deterioration rates

Results of the two-stage IPD meta-analysis replicated the findings of one-stage IPD on clinically significant deterioration (OR = 0.62; 95% CI 0.48 to 0.81, p < .001). Heterogeneity was zero. These results were replicated in sensitivity analysis on any deterioration rates showed similar outcomes and complete case analyses. There was no indication for publication bias across all the analyses. Finally, the examined study level variables were not significantly associated with clinically significant and any deterioration. Results of the two-stage IPD are presented in Table a. in Appendix F.

DISCUSSION

The present IPD meta-analysis aimed to examine the clinically significant symptom deterioration rates of self-guided iCBT compared to controls and to evaluate the moderating effects of deterioration. Of the 3806 participants included in the analysis, 7.2% showed clinically significant deterioration. Self-guided iCBT had low clinically significant deterioration

Table 3. Relative odds of deterioration under self-guided iCBT versus controls in one-stage IPD analysis

Variable	'Clinically significant deterioration'						'Any deterioration'					
	Full sample			Complete cases[b]			Full sample			Complete cases[b]		
	N_{obs} (N_{st})	OR (95% CI)	p	N_{obs} (N_{st})	OR (95% CI)	p	N_{obs} (N_{st})	OR (95% CI)	p	N_{obs} (N_{st})	OR (95% CI)	p
Main effects – deterioration												
Treatment group	3795 (13)	.62 (.46 – .83)	.001	2818 (13)	.61 (.46 – .83)	.001	3795 (13)	.65 (.55 – .76)	<.001	2818 (13)	.66 (.56 – .77)	<.001
Age												
Treatment group	3786 (13)	.36 (0.13 – 1.00)	.05	2809 (13)	3.22 (1.10 – 9.47)	.04	3786 (13)	.66 (.36 – 1.18)	.16	2809 (13)	1.48 (.38 – 1.22)	.20
Age*Treatment group		1.01(0.99 – 1.03)	.27		1.02 (1.00 – 1.04)	.19		1.00 (.98 – 1.02)	.96		1.00 (.98 – 1.02)	.93
Gender												
Treatment group	3788 (13)	.61(.43 – .87)	.008	2811 (13)	.61 (.42 – .88)	.008	3788 (13)	.61 (.50 – .74)	<.001	2811 (13)	.61 (.50 – 0.74)	<.001
Gender*Treatment group		1.02 (.58 – 1.80)	.96		1.05 (.58 – 1.89)	.87		1.20 (.86 – 1.67)	.28		1.27 (.89 – 1.81)	.18
Educational level												
Treatment group	2538 (10)	.57 (.23 – 1.44)	.23	1973 (10)	.59 (.23 – 1.52)	.28.	2538 (10)	.46 (.26 – .83)	.01	1973 (10)	.46 (.25 – .84)	.01
Educational level*Treatment group												
Secondary vs. primary education		1.48 (.51 – 4.26)	.48		.65 (.22 – 1.91)	.43		1.57 (.82 – 2.99)	.18		1.67 (.86 – 3.24)	.14
Tertiary vs. primary education		.99 (.34 – 2.91)	.98		.90 (.30 – 2.71)	.86		1.27 (.65 – 2.48)	.47		1.25 (.63 – 2.47)	.53
Relationship status												
Treatment group	3568 (12)	.58 (.37 – .91)	.02	2630 (12)	.59 (.38 – .92)	.02	3568 (12)	.61 (.48 – .80)	<.001	2630 (12)	.63 (.48 – .81)	<.001
Relationship status*Treatment group		1.15 (.64 – 2.07)	.63		1.12 (.78 – 1.59)	.71		1.02 (.75 – 1.40)	.88		1.01 (.71 – 1.44)	.96
Employment status												
Treatment group	3067 (10)	.66 (.40 – 1.09)	.11	2194 (10)	.70 (.41 – 1.18)	.18	3067 (10)	.55 (.40 – .77)	<.001	2194 (10)	.57 (.40 – .80)	.001
Employment status*Treatment group		.97 (.14 – 6.50)	.92		.92 (.48 – 1.76)	.82		1.22 (.83 – 1.81)	.32		1.21 (.80 – 1.83)	.36
Comorbid anxiety												
Treatment group	1728 (9)	.58 (.37 – .91)	.02	1447 (9)	.85 (.37 – .91)	.02	1728 (9)	.58 (.43 – .77)	<.001	1447 (9)	.57 (.42 – .76)	<.001
Comorbid anxiety*Treatment group		1.13 (.57 – 2.26)	.72		1.22 (.60 – 2.47)	.57		1.04 (.68 – 1.60)	.85		1.12 (.71 – 1.75)	.64
Baseline severity of depression												
Treatment group	3795 (13)	.61 (.44 – .85)	.003	2818 (13)	.61 (.44 – .85)	.003	3795 (13)	.65 (.54 – 0.77)	< .001	2818 (13)	1.51 (.56 – .79)	<.001
Baseline severity*Treatment group		.99 (.74 – 1.33)	.92		.99 (.72 – 1.35)	.93		1.06 (.91 – 1.24)	.46		1.11 (.94 – 1.29)	.21

N_{obs}: Number of observations; N_{st}: Number of studies; OR: Odds Ratio; SE: Standard error

[b] This is a sensitivity analysis that was conducted including only participants who completed post-treatment depression questionnaires

rates (5.8%) and resulted in lower risk of clinically significant deterioration compared to controls at the post-treatment assessment. Similar results were observed in sensitivity analyses. None of the examined participant- and study-level variables moderated clinically significant deterioration.

This is the first meta-analysis to have systematically examined deterioration rates in self-guided iCBT for adults with depressive symptoms. The finding that self-guided iCBT shows lower deterioration rates compared to controls is consistent with previous IPD meta-analysis of 2079 participants on guided internet based interventions (Ebert et al., 2016). According to this work, guided web-based interventions resulted in lower risk of clinically significant deterioration compared to controls. Furthermore, guided internet-based interventions showed 3.6% clinically significant deterioration, which is slightly lower but comparable to the present clinically significant deterioration rates of self-guided iCBT (5.8%) (Ebert et al., 2016). The deterioration rates found in the present IPD meta-analysis are in line with the deterioration rates observed in face-to-face treatment (5-10%) (Rozental et al., 2014) and considerably lower compared to the 12% rate of deterioration reported by a recent meta-analysis examining change under treatment as usual (Kolovos et al., 2017).

The present study has several notable strengths; we were able to obtain individual participant data from 3876 participants from the majority (81%) of the eligible trials. This large number of participants offered us adequate power to detect statistically significant differences between self-guided iCBT and controls on symptom deterioration rates and to examine moderators of clinically significant deterioration. In addition, the current sample of studies appears to be free from critical bias, since the included trials had high methodological quality. Other strengths of the current work are that heterogeneity between studies was small to moderate and there was no indication of publication bias.

Nevertheless, the current findings should be interpreted with caution due to a number of limitations. The present sample of studies is at (relatively low) risk of availability bias since three eligible studies were not available for inclusion. The published reports of these unavailable trials did not include deterioration rates. Thus, traditional meta-analysis of direct comparison between available and unavailable studies was not possible. However, results of a previous analysis showed no difference between the effectiveness of the available and unavailable studies, indicating that the present sample is representative (Karyotaki et al., 2017). In the present analysis missing outcome data were multiply imputed based on missing at random assumption. The missing at random assumption underlying multiple imputation is critical as it assumes that those participants for whom post-treatment data were imputed behaved similarly to those with post-treatment data with comparable profiles. Therefore, if individuals dropped out due to deterioration (missing not at random), this would not be captured and a conservative estimate of deterioration is likely. Nevertheless, we performed a complete case analysis to test the robustness of our main full sample analysis and we found no differences between full sample and complete cases in deterioration rates. Another limitation is that we could not examine

several variables that might influence deterioration, such as previous episodes of depression and symptom duration. Individuals who have experienced several episodes of depression in the past and those who have chronic symptoms might be at greater risk of deterioration. Moreover, the majority of the trials included recruited their participants through the community. Thus, the current findings cannot be generalised to patients treated in clinical settings since active care seekers may differ from individuals responding to advertisements.

From a clinical point of view, the present study has important implications. Although many patients prefer psychotherapy to antidepressants (D. J. van Schaik et al., 2004), pharmacotherapy dominates primary and secondary mental health care while psychotherapy is offered to a lesser degree. Self-guided iCBT has the potential to increase the availability and accessibility of psychotherapy and minimise the costs. However, the implementation of self-guided iCBT in clinical practice is hampered by barriers, such as concerns regarding its safety and effectiveness. The present study has demonstrated that self-guided iCBT results in lower risk for symptom deterioration compared to controls (including regular care services) and our previous study showed that is effective in treating depressive symptoms. This suggests that self-guided iCBT could be an alternative to watchful waiting in general practice and it can be disseminated at a large scale in countries where resources of mental health care are limited or inaccessible due to other reasons.

Symptom deterioration occurs in self-guided iCBT; thus, future studies should carefully examine and report deterioration rates. Future research on self-guided iCBT interventions should examine deterioration rates over longer time periods. Moreover, moderators, such as duration of symptoms and previous episodes, should be addressed by future studies to indicate for whom self-guided iCBT might be harmful. More studies from primary care are needed to replicate the current findings with clinical samples.

Conflict of interest

Dr Klein reported receiving funding for clinical trials (German Federal Ministry of Health, Servier), payments for presentations on internet interventions (Servier), and payments for workshops and books (Beltz, Elsevier and Hogrefe) on psychotherapy for chronic depression and psychiatric emergencies. No other disclosures were reported.

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09

CHAPTER 10

DOES INTERNET-BASED GUIDED SELF-HELP RESULT IN CLINICALLY RELEVANT CHANGES FOR PATIENTS WITH DEPRESSION? AN INDIVIDUAL PARTICIPANT DATA META-ANALYSIS

Karyotaki, E., Ebert, D.D., Donkin, L., Riper, H., Twisk, J., Burger, S., Rozental,A., Alfred Lange, A., Williams, A.P., Zarski, A.C., Geraedts, A., van Straten, A., Kleiboer, A., Björn Meyer, B., Burçin Ünlü Ince,B., Buntrock,C., Lehr, D., J. Snoek, F., Andrews, G. , Andersson, A., Isabella Choi, I., Ruwaard, J., Klein, J.P., Newby,J.M., Schröder, J., A.C. Laferton[2], J.A.C., van Bastelaar, K., Imamura, K., Vernmark, K., Boß, L., Sheeber, L.B., Kivi, M., Berking, M., Titov, N., Carlbring, P., Johansson, R., Kenter, R., Perini, S., Moritz, S., Nobis, S., Berger, T., Kaldo, V., Forsell, Y., Lindefors, N., Martin Kraepelien, M., Cecilia Björkelund, C., Kawakami, N., Cuijpers, P. (2017).

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ABSTRACT

Background:
Internet based guided self-help (IGSH) may increase the availability and accessibility of depression treatment. However, little is known about clinically relevant changes in IGSH for depression. Moreover, methodological and power limitations preclude the identification of patients groups that may benefit more from IGSH. This study aimed to investigate response rates, remission rates, and their moderators in randomized controlled trials (RCTs) comparing the effect of Internet-based guided self-help interventions for adult depression to control groups using an individual patient data meta-analysis approach.

Method:
Literature searches in PubMed, Embase, PsycINFO and Cochrane Library resulted in 13,384 abstracts from database inception to January 1, 2016. Twenty-four RCTs (4889 participants) comparing an IGSH treatment with a control group contributed data to the analysis. Missing data were multiply imputed. To examine treatment outcome on response and remission, mixed-effects models with participants nested within studies were used. Beck. Response and remission rates were calculated per study and outcome measure separately using the Reliable Change Index.

Findings:
The intervention group obtained significantly higher response rates (OR = 2.49, 95% CI 2.17 – 2.85) and remission rates compared to controls (OR = 2.41, 95% CI 2.07 – 2.79). The moderator analysis indicated that older participants (OR = 1.01) and native-born participants (1.66) were more likely to respond to treatment compared to younger participants and ethnic minorities respectively. Age (OR = 1.01) and ethnicity (1.73) also moderated the effects of treatment on remission. Moreover, adults with more severe depressive symptoms at baseline were more likely to remit after receiving internet-based treatment (OR = 1.19).

Interpretation:
IGSH interventions lead to substantial positive treatment effects on treatment response and remission at post-treatment. Thus, such interventions may complement existing services for depression and potentially reduce the gap between the need and provision of evidence-based treatments.

INTRODUCTION

Major Depressive Disorder (MDD) is highly prevalent (Alonso et al., 2004b; Kessler et al., 2005; Waraich, Goldner, Somers, & Hsu, 2004) and associated with substantial impairment (Saarni et al., 2007; Üstün, Ayuso-Mateos, Chatterji, Mathers, & Murray, 2004a) and economic costs (Berto, D'Ilario, Ruffo, Virgilio, & Rizzo, 2000; Greenberg & Birnbaum, 2005; F. Smit et al., 2006). Psychological treatments have been shown to be effective in the treatment of depression (Cuijpers et al., 2014; Cuijpers, Annemieke van Straten, et al., 2008a). However, the majority of depressed people remain untreated (Kohn, Saxena, Levav, & Saraceno, 2004; Wittchen et al., 2011), even in high income countries (Mack et al., 2014; Smith et al., 2013) and especially in rural areas (Kessler et al., 2001).

Using the Internet to provide guided self-help interventions may help overcome some of the limitations of traditional treatment services (Andersson & Titov, 2014; Ebert, Lehr, Baumeister, et al., 2014). Internet-based guided self-help interventions (IGSH) (a) provide high accessibility, (b) may attract people who do not use traditional mental health services, and (c) are easily scalable. A recent meta-analysis (MA) showed that IGSH for depression can have positive effects on depressive symptoms (Richards & Richardson, 2012). However, statistical comparisons based on group means provide limited information about clinical significance (Jacobson & Truax, 1991). Therefore, response and remission have been suggested as the outcome criteria of choice for depression treatment (Keller, 2003; Rush et al., 2006). Remission is generally considered a state in which symptoms of the illness are (nearly) absent (Rush et al., 2006). It is associated with better functioning (Hirschfeld et al., 2002; Riso et al., 1997), lower relapse rates, and improved long-term prognosis (Bech, Lönn, & Overø, 2010; Fava, Fabbri, & Sonino, 2002; Karp et al., 2004; Kennard et al., 2009; Ogrodniczuk, Piper, & Joyce, 2004; Taylor, Walters, Vittengl, Krebaum, & Jarrett, 2010). It is the accepted goal of treatment of acute depression (Anderson et al., 2008; Gelenberg et al., 2010; Lam et al., 2009; NICE, 2010; Thase & Ninan, 2001). However, while not all patients achieve remission (Cuijpers et al., 2014), some may still be classified as responders, i.e. achieve a clinically significant reduction in depressive symptoms (Frank et al., 1991).

Neither remission nor response has been addressed in any meta-analyses of IGSH for depression (Andersson & Cuijpers, 2009; Andersson, Cuijpers, Carlbring, Riper, & Hedman, 2014b; Andrews et al., 2010; Johansson & Andersson, 2012; Richards & Richardson, 2012). Inconsistencies in methodology for defining response and remission as well as missing reports of these outcomes in studies hinder their evaluation using conventional meta-analytic approaches. Another issue not yet addressed is the possibility that not all subgroups of patients benefit from this specific treatment delivery. For example, it may be argued that patients with severe symptoms are too impaired to gain substantial effects in terms of remission/response with IGSH (Kiluk et al., 2011). Consequently, the only treatment guideline that currently include IGSH [UK NICE guidelines (NICE, 2010)] recommends its use only for mild-to-moderate symptoms (NICE, 2010). Other subgroups of participants, such as those with low education,

may not be able to apply therapeutic self-help strategies and thus, respond poorly (Warmerdam, van Straten, Twisk, & Cuijpers, 2013), and older adults may have difficulties in utilizing Internet-based technologies (Donker et al., 2013).

Given that the number of people from specific subgroups is often small in single trials, and randomized trials are usually powered to detect overall treatment effects, RCTs are mostly underpowered to adequately examine subgroup and moderator analysis (Brookes et al., 2004). As studies also seldom report effectiveness for different patient characteristics, it is impossible to examine patient-level moderators using traditional meta-analytic approaches. Individual participant data meta-analyses (IPD MA) can overcome some of the limitations of the conventional study level MAs (Clarke, 2005; Jones, Riley, Williamson, & Whitehead, 2009; Riley et al., 2010). By pooling the raw data of individual trials, it is possible to conduct analyses not reported in original studies and obtain large sample sizes with sufficient power to both examine effects in relevant subgroups and identify outcome moderators (Cooper & Patall, 2009).

The present study aimed to examine response and remission rates in randomized controlled trials for the effect of IGSH on adult depression at the post-treatment by using an IPD MA approach. Additionally, the effects on response and remission were evaluated in specific subgroups of interest and tested for potential moderating effects.

METHODS

Identification and selection of studies

We included randomized trials in which the effects of an IGSH treatment were compared with a comparison group (waiting list, care-as-usual, other) in adults with acute depression. Studies were excluded if interventions were provided without guidance**, if** they were delivered to the individual via a group format, or if they required the individual to travel to use the program (e.g., a clinic). No language restrictions were applied. Figure 1 shows the selection process for the included studies. For the identification of potential studies for inclusion, we used a database of 1,885 papers on the psychological treatment of depression described in detail elsewhere (Cuijpers, van Straten, Warmerdam, et al., 2008). For this database, a literature search was conducted for studies published from database inception to January 2016 [see Supplement - Search Strings for PubMed (Chapters 2-4 & 6-10)]. This yielded a further 4562 abstracts in PubMed, 2530 in PsycINFO, 4243 in Embase, and 5072 in the Cochrane Library for review.

Data collection

Corresponding authors were contacted for each of the identified papers and were asked to provide raw data from their study and whether they were aware of other RCTs that met our inclusion criteria but were not yet published. Of the 27 studies identified from the search, data were obtained from 24 (Andersson et al., 2005; Berger, Hammerli, et al., 2011; Buntrock et al., 2015; Carlbring et al., 2013; I. Choi et al., 2012; Ebert, Lehr, Boß, et al., 2014; Geraedts et al., 2014; Hallgren et al., 2015; Imamura et al., 2014; Johansson, Ekbladh, et al., 2012; Johansson

et al., 2012; Kenter, Cuijpers, Beekman, & van Straten, 2016; Kivi et al., 2014; Klein et al., 2016; Newby et al., 2013; Nobis et al., 2015; Perini, Titov, & Andrews, 2009; Ruwaard et al., 2009; Sheeber et al., 2012; Unlu Ince et al., 2013; van Bastelaar, Pouwer, Cuijpers, Riper, & Snoek, 2011; Vernmark, Lenndin, Bjarehed, et al., 2010; Warmerdam, van Straten, Twisk, Riper, & Cuijpers, 2008; Williams, Blackwell, Mackenzie, Holmes, & Andrews, 2013). Data from three studies (Titov et al., 2015; Titov et al., 2011; Williams, Wilson, Morrison, McMahon, Andrew, Allan, et al., 2013) could not be obtained.

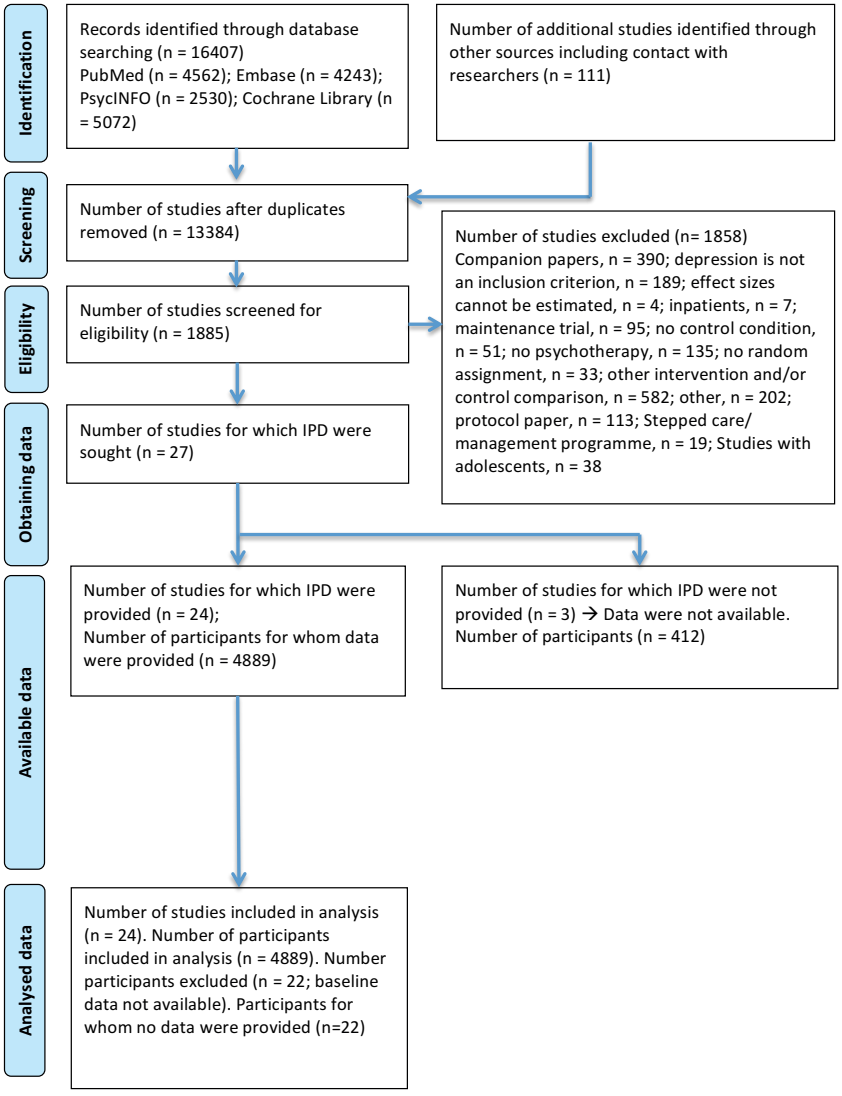


Figure 1. PRISMA IPD Diagram of studies selection process

Risk of bias assessment

The validity of the included studies was assessed using four criteria from the Cochrane 'Risk of Bias' assessment tool (Higgins & Altman, 2008). This tool identifies possible sources of bias, including: the adequate generation of allocation sequence, the allocation concealment, the prevention of knowledge of the allocated intervention, and dealing with incomplete outcome data (this was assessed as positive when intention-to-treat analyses were conducted, meaning that all randomized patients were included in the analyses). Two researchers conducted the quality assessment independently.

Calculating response and remission rates

The majority of the studies used either the Center for Epidemiological Studies Depression Scale [CES-D (Radloff, 1977)] or the Beck Depression Inventory I or II [BDI-I (Beck et al., 1961); BDI-II (Beck, Steer, & Brown, 1996)] as an outcome measure. Two studies used the Patient Health Questionnaire–9 [PHQ-9 (Kroenke, Spitzer, & Williams, 2001)] and the Montgomery–Asberg Depression Rating Scale [MADRS (Davidson, Turnbull, Strickland, Miller, & Graves, 1986)], respectively. For all measures, we calculated response rates according to the widely used Reliable Change Index (Jacobson & Truax, 1991). Reliable change was calculated separately for each included study using the standard deviation at baseline and the test-retest reliability coefficient of the measures [CES-D: 0.87 (Miller, Anton, & Townson, 2008); BDI-I: 0.72 (Yin & Fan, 2000); BDI-IA: 0.82 (Beck, Steer, & Carbin, 1988); BDI-II: 0.93 (Beck & Steer, 1984); PHQ-9: 0.76 (Kroenke et al., 2001); MADRS: 0.78 (Fantino & Moore, 2009)]. In the absence of reliable cut-off scores for remission and in order to maintain consistency in defining remission across different measures, we applied Jacobson's method to define a near symptom-free state (Jacobson & Truax, 1991). Accordingly, patients were classified as remitters if they moved two standard deviations below the mean of the clinical group in each study. The resulting cut-off scores represent a rather high-end state of functioning.

To test the robustness of our main findings, we conducted sensitivity analyses applying alternative criteria for response and remission. For response, we chose 50% symptom improvement (a relative instead of an absolute improvement; Rush et al., 2006). For remission, we used established cut-offs for the outcome measures (BDI-I <13; BDI-II <10; CESD <16; PHQ-9 < 5 and MADRS < 7).

Missing data

Analyses were conducted according to the intention-to-treat principle. Missing data were handled using the missing-at-random assumption (100 imputations). In addition, we performed a complete case analysis using data from participants who completed post-treatment assessment.

Multiple treatments within one study

In two studies two treatments were compared to a single control group (R. Johansson, E. Sjˆberg, et al., 2012; L. Warmerdam, Straten, Twisk, Riper, & Cuijpers, 2008). In these cases, we treated

each comparison as a separate study and avoided double counting of controls by randomly assigning half of the controls to each comparison.

IPD meta-analysis

Effects were calculated using the one-stage IPD MA approach where we merged all individual participant data from the available studies with participants clustered on studies (Riley et al., 2010). One-stage IPD MA approach is preferred because it allows for a more sophisticated modelling of covariates compared to two-stage IPD MA approach. All analyses were conducted with Stata (version 14.2) (*Stata Statistical Software: Release 13*, 2015). We performed a logistic multilevel analysis to examine the effect of guided Internet based interventions on response and remission rates. Response and remission were used as dependent variables and treatment group was used as the independent variable. A random intercept for study was added to each model.

We examined baseline individual-level variables (age, gender, educational level, ethnicity, relationship status, employment status, comorbid anxiety, baseline depression severity, previous depressive episodes, medication use and alcohol use) to explore their moderating effects on treatment outcomes. Response and remission were used as outcome variables and each of the aforementioned baseline variables and treatment group were used as independent variables. We added the interaction between each examined variable and treatment group into the multilevel mixed effect logistic regression model.

In addition to the one-step IPD MA, we also performed a two-stage IPD MA to test the robustness of our findings and to examine several additional study-level variables of interest (diagnosis, target group, type of control, recruitment, outcome measure, number of online sessions, intervention type and risk of bias). We first calculated event rates for each study separately based on the imputed data. Then, pooled event rates across studies were calculated using a random-effect model as implemented in the Comprehensive MA software package, which accounts for between-study heterogeneity (Abo-Zaid et al., 2013). We proceeded to calculate the odds ratio (OR) for each study, and pooled the results across the studies using a random-effects DerSimonian-Laird model (DerSimonian & Laird, 1986). For our main outcomes we also calculated the numbers needed to treat (NNT) and their 95%-confidence intervals as compared to the control groups (Laupacis, Sackett, & Roberts, 1988).

To test study-level moderators we conducted a series of subgroup-analyses, using the mixed-effect model. The following subgroups were investigated: *Study characteristics:* MDD confirmed using an established diagnostic interview (yes/no), type of control group (non-active/active); recruitment (community/clinical setting); recruitment location; outcome measure (BDI/other); risk of bias (low [4]/some risk [<4]), *Intervention characteristics:* intervention type (Cognitive Behaviour Therapy (CBT)/other), number of modules (4-5/6-7/≥8).

We calculated the I^2-statistic as an indicator of heterogeneity (Ioannidis & Trikalinos, 2007). A value of 0% indicates no observed heterogeneity, 25% low, 50% moderate, and 75% high heterogeneity. We calculated 95% confidence intervals using the non-central chi-squared-based approach (Stata) (Orsini et al., 2006). We also calculated the Q-statistic, but only report whether this was significant.

Publication bias was examined by inspecting the funnel plot, by Egger's test (Matthias Egger et al., 1997) and Duval and Tweedie's trim-and-fill procedure (Duval & Tweedie, 2000), which yields an estimate of the effect size after publication bias has been taken into account (Borenstein et al., 2009).

RESULTS

Characteristics of included studies & participants

A total of 4889 cases were included from 24 studies (26 comparisons) conducted in 7 different countries. Table a. (Appendix G1) displays selected study characteristics, and Table b shows patient characteristics (Appendix G1). MDD was confirmed using a diagnostic interview in 15 studies. Most interventions were based on CBT (n=17) or Problem-Solving Therapy (PST) (n=6). The most common control was non-active delayed access to the program (n=13), but in eleven studies, an active comparison (brief scheduled therapist support, web-based discussion groups or treatment as usual) was used as control.

Overall, risk of bias was low. All studies reported an adequate sequence generation and allocation to conditions by an independent party. Twenty studies reported blinding of outcome assessors or used only self-report outcomes. All studies were coded as having handled missing data adequately, as intention-to-treat analyses were applied. Twenty met all four-quality criteria, while the remaining five met three out of four criteria. Agreement between independent raters on the risk of bias was 95% across studies.

One stage IPD – response

Overall effects on response are presented in Table 1. At post-treatment the pooled response rate was 56.19% (95% CI 53.99 – 58.38%) in the intervention and 35.13% (95%CI: 33.07 – 37.20%) in the control conditions. Response rates were significantly higher in the intervention groups compared to controls, with an OR of 2.49 (95% CI: 2.17-2.85; $p < .001$ and NNT = 4.74, 95% CI = 4.21 – 5.46). Comparable results were found in the complete case analysis. Applying the alternative response criteria (50% symptom reduction) resulted in lower response rates in both the intervention (39.63%, 95% CI 37.49 – 41.77) and control conditions (19.12%, 95% CI 17.39 – 20.85), but the effect was slightly higher (OR = 2.83, 95% CI 2.45 – 3.28; $p = .000$).

Moderator analysis showed that the effect of IGSH on response was higher in native-born participants compared to ethnic minorities (OR = 1.66, 95% 1.07 – 2.59; $p = 0.02$), and in

participants in a relationship compared to single adults (OR = 1.33, 95% CI; 1.01 – 1.74). We also found that older adults responded better compared to younger adults (OR of age = 1.01, 95% CI 1.00 – 1.02; p =0.03). Baseline severity moderated treatment outcome in the complete case analysis but not in the intention to treat analysis, although there was a trend suggesting that more severe depression may be associated with better outcome (OR = 1.16, 95% CI 1.00 – 1.35; p = 0.05). None of the other examined variables moderated the effects of treatment on response.

One stage IPD – remission

Mean remission rates at post-treatment across 26 comparisons were 38.51% (95% CI: 36.35 – 40.68) in the intervention and 21.52% (95% CI: 19.74 – 23.31) in the control conditions leading to an OR of 2.41 (95% CI 2.07 - 2.79; p < .001) and NNT = 5.98, 95% CI 4.35 – 6.80). Complete case analysis revealed similar outcomes. The alternative remission criteria resulted in slightly higher rates (intervention: 41.98%; 95% CI 39.74 – 44.2; control: 26.40%; 95% CI 24.40 – 28.23) and a slightly higher OR of 2.17 (95% CI 1.89 – 2.49; p < .001).

Moderator analyses resulted in similar findings as the ones found for response. Age (OR = 1.01, 95% CI 1.00 – 1.03; p = 0.02), ethnicity (OR = 1.73, 95% CI 1.07 – 2.81; p = 0.03) and baseline depression severity (OR = 1.19, 95% CI 1.01 – 1.39; p = 0.04) significantly moderated effect on remission. However, relationship status was not a significant moderator of remission (p = 0.31). Problematic alcohol drinking moderated response in the complete case analysis but not in the intention to treat analysis. None of the other variables moderated the effect of treatment on remission rates

Two stage IPD – response

Results of the two-stage IPD showed similar results as those of the one-stage IPD on response rates (Table c, Appendix G1). Effects on response rates at post-treatment were significant and in favor of Internet-based treatments (OR = 2.76, 95% CI 2.23 – 3.41; p < .001). The NNT was 4.16 (95% CI: 3.41 – 5.26). Heterogeneity was moderate I^2 = 58% (95% CI 35 – 73). Inspection of the funnel plot and Egger's test indicated some possible publication bias. After adjustment for missing studies (8 imputed studies) using the Duval-Tweedie trim-and-fill procedure, OR for response at post-test was 2.15 (95% CI 1.72 – 2.70). Complete case analysis resulted in similar outcomes. Effects on response were significantly moderated by type of control groups in complete case analysis (higher effects of waiting list groups compared to active control groups; p = 0.02), but this was not replicated in the intention to treat analysis (p = 0.05). All other differences in effects estimates between subgroups on response were non-significant in both intention to treat and complete case analyses (Table 2).

Table 1. Relative odds of response and remission under guided psychotherapy versus controls in one-stage IPD analysis

	Response						Remission					
	Full sample			Complete cases[b]			Full sample			Complete cases[b]		
Variable	**N_{obs} (N_{st})**	**OR (95% CI)**	**p**	**N_{obs} (N_{st})**	**OR (95% CI)**	**p**	**N_{obs} (N_{st})**	**OR (95% CI)**	**p**	**N_{obs} (N_{st})**	**OR (95% CI)**	**p**
Main effects – treatment outcome												
Treatment group	4867 (26)	2.49 (2.17 – 2.85)	<.001	3878 (26)	2.49 (2.17 - 2.86)	<.001	4867 (26)	2.41 (2.07 - 2.79)	<.001	3878 (26)	2.41 (2.08 - 2.79)	<.001
Age												
Age in years (continuous)	4858 (26)	0.32 (0.31 – 0.33)	.00	3869 (26)	0.98 (0.97 – 0.99)	.001	4858 (26)	0.99 (0.98 – 1.00)	.01	3869 (26)	0.98 (0.98 – 1.00)	.006
Treatment group		1.53 (0.93 – 2.50)	.09		1.42 (0.85 – 2.38)	.17		1.31 (0.76 – 2.25)	.33		1.13 (0.65 – 1.96)	.67
Age*Treatment group		1.01 (1.00 – 1.02)	.03		1.01 (1.00 – 1.02)	.03		1.01 (1.00 – 1.03)	.02		1.02 (1.01 – 1.03)	<.001
Gender												
Male gender	4858 (26)	0.72 (0.37 – 1.38)	.32	3869 (26)	0.76 (0.62 – 0.95)	.01	4858 (26)	0.87 (0.69 – 1.11)	.26	3869 (26)	0.95 (.75 – 1.21)	.70
Treatment group		2.45 (2.07 – 2.91)	<.001		2.47 (2.08 – 2.94)	<.001		2.35 (1.94 – 2.84)	<.001		2.38 (1.97 – 2.88)	<.001
Gender*Treatment group		1.03 (0.79 – 1.35)	.83		1.01 (0.76 – 1.34)	.93		1.06 (0.79 – 1.41)	.72		1.03 (0.76 – 1.39)	.87
Educational level												
Secondary educational level	3461 (20)	0.72 (0.40 – 1.28)	.26	2821 (20)	0.67 (0.37 – 1.22)	.19	3461 (20)	1.42 (0.63 – 3.21)	.40	2821 (20)	1.71 (0.72 – 4.08)	.22
Tertiary educational level		0.80 (0.52 – 1.24)	.32		0.78 (0.44 – 1.38)	.40		1.35 (0.61 – 2.96)	.46		1.65 (0.71 – 3.86)	.25
Treatment group		1.84 (0.95 – 3.56)	.07		1.52 (0.76 – 3.04)	.24		2.20 (0.90 – 5.39)	.09		2.45 (0.92 – 6.50)	.07
Secondary vs. primary education*treatment group		1.76 (0.86 – 3.62)	.12		2.17 (1.02 – 4.61)	.04		1.24 (0.48 – 3.19)	.66		1.14 (0.41 – 3.19)	.80
Tertiary vs. primary education*treatment group		1.47 (0.74 – 2.93)	.28		1.75 (0.85 – 3.58)	.13		1.11 (0.44 – 2.80)	.82		0.97 (0.36 – 2.63)	.95
Ethnicity												
Native-born participants	1936 (8)	0.78 (0.51 – 1.20)	.26	1563 (8)	0.73 (0.47 – 1.13)	.16	1936 (8)	0.84 (0.51 – 1.37)	.55	1563 (8)	0.78 (0.47 – 1.31)	.35
Treatment group		1.88 (1.37 – 2.57)	<.001		1.58 (1.14 – 2.21)	.01		1.90 (1.40 – 2.59)	<.001		1.59 (1.14 – 2.20)	.01
Ethnicity*Treatment group		1.66 (1.07 – 2.59)	.02		2.01 (1.28 – 3.17)	<.001		1.73 (1.07 – 2.81)	.03		2.23 (1.33 – 3.73)	<.001

continued

Table 1. Relative odds of response and remission under guided psychotherapy versus controls in one-stage IPD analysis (continued)

	Response						Remission					
	Full sample			Complete cases[b]			Full sample			Complete cases[b]		
Variable	**N_{obs} (N_{st})**	**OR (95% CI)**	**p**	**N_{obs} (N_{st})**	**OR (95% CI)**	**p**	**N_{obs} (N_{st})**	**OR (95% CI)**	**p**	**N_{obs} (N_{st})**	**OR (95% CI)**	**p**
Relationship status												
In a relationship	4479	0.88 (0.71 – 1.07)	.20	3595	0.83 (0.68 – 1.03)	.10	4479	1.08 (0.85 – 1.36)	.55	3595	1.07 (0.84 – 1.38)	.57
Treatment group	(25)	2.12 (1.74 – 2.59)	<.001	(25)	1.98 (1.61 – 2.43)	<.001	(25)	2.20 (1.78 – 2.72)	<.001	(25)	2.12 (1.70 – 2.63)	<.001
Relationship status*Treatment group		1.33 (1.01 – 1.74)	.04		1.50 (1.13 – 2.00)	.01		1.17 (0.87 – 1.57)	.31		1.24 (0.91 – 1.68)	.18
Employment status												
Employed	4212	1.00 (0.78 – 1.28)	.99	3367	1.08 (0.83 – 140)	.56	4212	1.14 (0.85 – 1.53)	.39	3367	1.23 (0.91 – 1.67)	.18
Treatment group	(19)	2.41 (1.79 – 3.26)	<.001	(19)	2.47 (1.80 – 3.40)	<.001	(19)	2.12 (1.50 – 2.99)	<.001	(19)	2.17 (1.52 – 3.10)	<.001
Employment status*Treatment group		0.97 (0.69 – 1.37)	.88		0.94 (0.66 – 1.34)	.74		1.11 (0.76 – 1.63)	.61		1.06 (0.71 -1.58)	.78
Comorbid anxiety												
Existence of comorbid anxiety	2332	1.19 (0.91 – 1.54)	.20	1885	1.15 (0.87 – 1.52)	.31	2332	0.86 (0.63 – 1.15)	.31	1885	0.81 (0.60 – 1.11)	.19
Treatment group	(10)	2.19 (1.65 – 2.89)	<.001	(10)	2.19 (1.64 – 2.94)	<.001	(10)	2.11 (1.57 – 2.82)	<.001	(10)	2.10 (1.55 – 2.85)	<.001
Comorbid anxiety*Treatment group		1.25 (0.86 – 1.81)	.25		1.28 (0.87 – 1.88)	.21		1.09 (0.74 – 1.63)	.66		1.12 (0.74 – 1.69)	.58
Baseline severity of depression												
Depressive symptoms (continuous)	4867	1.79 (1.61 – 1.99)	<.001	3878	1.77 (1.58 – 1.97)	<.001	4867	0.48 (0.42 – 0.55)	<.001	3878	0.46 (0.37 – 0.49)	<.001
Treatment group	(26)	2.61 (2.26 – 3.00)	<.001	(26)	2.65 (2.30 – 3.06)	<.001	(26)	2.67 (2.28 – 3.13)	<.001	(26)	2.68 (2.28 – 3.15)	<.001
Baseline severity*Treatment group		1.16 (1.00 – 1.35)	.05		1.22 (1.04 – 1.42)	.01		1.19 (1.01 – 1.39)	.04		1.25 (1.06 – 1.48)	.01
Previous depressive episodes												
One or more previous episodes	389	1.12 (0.97 – 1.29)	.13	288	1.12 (0.97 – 1.29)	,12	389	1.00 (0.94 – 1.08)	.91	288	1.01 (0.93 – 1.08)	.87
Treatment group	(4)	2.83 (1.62 – 4.96)	<.001	(4)	3.05 (1.70 – 5.46)	<.001	(4)	2.84 (1.61 – 5.02)	<.001	(4)	3.19 (1.82 – 5.93)	<.001
Previous episodes*Treatment group		0.93 (0.77 – 1.12)	.43		0.93 (0.77 – 1.12)	.47		0.99 (0.88 – 1.12)	.91		0.98 (0.87 – 1.11)	.75

continued

Table 1. Relative odds of response and remission under guided psychotherapy versus controls in one-stage IPD analysis (continued)

	Response						Remission					
	Full sample			Complete cases[b]			Full sample			Complete cases[b]		
Variable	**N_{obs} (N_{st})**	**OR (95% CI)**	**p**	**N_{obs} (N_{st})**	**OR (95% CI)**	**p**	**N_{obs} (N_{st})**	**OR (95% CI)**	**p**	**N_{obs} (N_{st})**	**OR (95% CI)**	**p**
Medication use												
Use of antidepressants	3793	1.12 (0.86 – 1.45)	.39	3044	1.08 (0.82 – 1.43)	.56	3793	1.01 (0.75 – 1.38)	.93	3044	0.94 (0.69 – 1.29)	.73
Treatment group	(19)	2.59 (2.16 – 3.11)	<.001	(19)	2.53 (2.10 – 3.05)	<.001	(19)	2.38 (1.96 – 2.90)	<.001	(19)	2.38 (1.95 – 2.89)	<.001
Medication use*Treatment group		0.83 (0.59 – 1.15)	.26		0.82 (0.58 – 1.15)	.25		0.82 (0.58 – 1.17)	.27		0.80 (0.56 – 1.15)	.23
Alcohol use												
Problematic alcohol drinking	1325	0.66 (0.40 – 1.08)	.10	984	0.62 (0.36 – 1.04)	.07	1325	0.76 (0.42 – 1.38)	.37	984	0.74 (0.40 -1.36)	.33
Treatment group	(5)	1.71 (1.29 – 2.25)	<.001	(5)	1.49 (1.12 – 2.00)	.01	(5)	1.85 (1.39 – 2.46)	<.001	(5)	1.80 (1.34 – 2.43)	<.001
Alcohol use*Treatment group		1.53 (0.80 – 2.93)	.20		2.08 (1.04 – 4.17)	.04		1.91 (0.94 – 3.89)	.07		2.49 (1.17 – 5.29)	.02

N_{obs}: Number of observations; CI: Confidence Intervals; N_{st}: Number of comparisons; OR: Odds Ratio

[b] This is a sensitivity analysis that was conducted including only participants who completed post-treatment depression questionnaires

Two-stage IPD – remission

Table c (Appendix G1) shows the results of the two-stage IPD analyses on remission rates. Remission rates at the post-treatment were significantly higher in the intervention groups compared to control groups, with an OR of 2.80 (95% CI 2.21 – 3.56; p < .001) and a NNT of 5.26 (95% CI 4.34 – 6.66). Heterogeneity was moderate (I^2 = 54%, 95% CI 29 – 71). There was some indication of publication bias. Duval-Tweedie trim-and-fill procedure resulted in 7 missing studies. The adjusted OR was 2.17 (95% CI 1.90 – 2.48). Eggers test was significant (p <0.05). Complete case analysis showed similar outcomes. Subgroup analysis did not result in significant associations. Tables a. and b. in Appendix G2 show the forest plots of remission and response respectively.

DISCUSSION

This IPD MA provides a precise estimation of the overall and specific subgroup effects of internet-based guided self-help on response and remission. Effects on response were within the range of effects found in a recent meta-analysis for face-to-face psychotherapy (Cuijpers et al., 2014). Remission rates were slightly lower both in the intervention (38.51%) and in the control conditions (21.52%) compared to face-to-face psychotherapy (43% vs. 27%; HAM-D_{17} cut-off for "no depression"< 7). However, when using the alternative remission criteria based on cut-offs for no depression on the examined scales, which is more comparable to the criteria used in the MA for face-to-face psychotherapy, remission rates were similar (41.98% vs. 26.40%).

Older adults and individuals with more severe depressive symptoms were found to have significantly higher remission and response rates. These findings are of particular importance as these patient groups are often underrepresented in Internet intervention trials; it was until now unclear whether results from randomized trials could be generalized to these populations (Andersson & Titov, 2014). Different engagement levels between older and younger adults may explain the better outcomes for older adults. A recent IPD meta-analysis on unguided interventions showed that younger adults have higher risk of treatment dropout compared to older adults (Karyotaki et al., 2015). It should, however, be noted that age had a small moderation effect (as age increases by 10 years, the odds of responding/remitting after IGSH increases by 0.10 units). Moreover, the substantial effects found for the severely depressed individuals are in line with the findings of the IPDMA of Bower et al. (2013) of low-intensity interventions (Bower et al., 2013). This result may reflect differences in motivation, as severely depressed adults may be more motivated to engage with the treatment.

Ethnicity was also found to moderate outcome. Ethnic minorities had significantly lower response and remission rates than natives. Cultural adaptations may be needed to serve the needs of ethnic minority groups. Perhaps the interventions are not enough adapted to suit the needs of the different minorities. Moreover, patients with a partner had significantly better outcomes than those without, suggesting possibly that partners may actively support patients during treatment or the feeling of loneliness may predispose single adults to benefit less. This

result contrasts findings from a recent IPDMA of unguided web-based CBT for depression (Karyotaki, Riper, Twisk, & et al., 2017). This difference in findings between the two IPDMAs may be partly explained by differences in the nature of guided and unguided Internet-based interventions or in differences between baseline participant characteristics.

When interpreting results from this study, several limitations must be considered. First, although we were able to include all but three of the identified trials (24/27 studies), availability bias cannot be ruled out. Second, we were only able to test for effects and effect modifiers when sufficient information was available across studies. Thus, there may be other relevant patient-characteristics associated with differential effects of IGSH treatment, where such treatment is less or possibly not effective at all [i.e. chronic depression (de Maat, Dekker, Schoevers, & de Jonghe, 2007) or comorbid personality disorders (Newton-Howes, Tyrer, & Johnson, 2006)]. Third, although two studies (Choi et al., 2012; Unlu Ince et al., 2013)were directed at ethnic minorities (Turkish and Chinese migrants), all studies were conducted in Western, high-income countries. Thus, results may not be generalizable to low and middle-income countries. Fourth, most of the studies recruited participants through the community. Therefore, the generalizability of the current findings to clinical samples is limited. However, we did not find any indication that the way of recruitment was associated with effects. Fifth, in our analyses we observed moderate heterogeneity that could not be fully explained by the examined sub-group analyses. Sixth, there was some indication of publication bias, showing that the current analysis may have over-estimated effects because studies with negative results remained unpublished. However, after adjusting for missing studies, results remained significant and in favour of IGSH.

CONCLUSIONS

The present study has implications for research, clinical practice, and policy. The substantial effects on response and remission strongly support the use of Internet-based guided self-help treatments for depression as an evidence-based treatment option in routine care. Therefore, the use of IGSH could be a valuable strategy to bridge the gap between the demand for psychological interventions and the supply available (Kohn et al., 2004). Also, the current results indicate that the application of such interventions does not need to be restricted to certain patient populations (i.e. patients with mild-to-moderate symptoms), which is currently recommended by the NICE clinical guideline (NICE, 2010). IGSH could very well be used as a first step in a stepped-care approach (Bower et al., 2013; van Straten, Hill, Richards, & Cuijpers, 2015). In these approaches, a less resource-intensive treatment, such as IGSH, can first be offered, with those patients not responding in IGSH subsequently referred to more intensive psychological treatments. Since psychotherapists trained in evidence-based methods are a limited resource, IGSH treatment can help allocate face-to-face therapy to those most in need of intensive care. However, given that (a) acceptance of an intervention by the target population is always a necessary prerequisite for utilizing interventions(Andrade et al., 2014; Baumeister, Nowoczin, et al., 2014; D. Ebert et al., 2015), (b) studies indicate that different patients may prefer different types of treatment modalities (i.e. face-to-face psychotherapy,

medications, guided self-help (Musiat, Goldstone, & Tarrier, 2014; van Schaik et al., 2004) and (c) preferences may affect treatment uptake utilization and outcome (Kwan, Dimidjian, & Rizvi, 2010), we nevertheless caution that IGSH should only be offered as one treatment alternative alongside other evidence-based options.

It should further be acknowledged that depending on the criteria, between 44-61% of the participants did not show response, and 58%-62% percent did not achieve remission. It may be the case that a subgroup of these patients would have benefited from other forms of treatment. Also, if initial patient treatment expectations are not met in one treatment modality, it may adversely affect general treatment expectations, which may impact the likelihood that these patients engage in or benefit from different future treatment deliveries (Ebert, Lehr, Baumeister, et al., 2014; Rozental et al., 2014). However, this is a yet unanswered question that should be addressed in future studies. Finally, this study also indicates that more research is needed to determine the effectiveness of IGSH (a) for specific subgroups of patients in the long-term, (b) for patients in non-Western and low/middle-income countries, (c) for specific conditions such as comorbid general medical disorders (Nobis et al., 2013) and (d) in relation to different theoretical treatment modalities and patient-characteristics (e.g. cognitive therapy vs. behavioral activation in severe depression or old age).

In conclusion, the present study provides evidence that IGSH is an effective treatment for depression in patients with a wide range of characteristics and may thus complement existing services.

PART IV

General Disucssion

CHAPTER 11

GENERAL DISCUSSION

INTRODUCTION

Although there is a growing body of literature on psychotherapy effectiveness, there are still many clinically relevant questions that remain unanswered. Little is known about the long-term effects of psychotherapy alone or in combination with antidepressant medications. Moreover, it is still not clear whether psychotherapeutic interventions developed in high-income countries are also effective in low- and middle-income countries. It is also unclear if psychotherapeutic interventions are cost effective. With regard to purely self-guided Internet based psychotherapy, further research is needed to give the best estimate of these interventions, to evaluate possible negative effects and to examine which factors influence the dropout rates. Regarding guided web-based interventions, very little is known about important additional clinical outcomes, such as remission and response rates. The present thesis aimed at improving current knowledge on the effectiveness of psychotherapy by reviewing existing research evidence though a series of systematic reviews and meta-analyses. In this chapter, the key findings and limitations of this thesis as well as implications for future research and clinical practice are discussed. Overall conclusions are given at the end of this chapter.

KEY FINDINGS

Psychotherapy alone or combined with antidepressants results in enduring effects

Currently, maintenance pharmacotherapy is the most widely used first-step treatment approach to prevent a relapse of depression. However, many patients with depression prefer to receive pharmacotherapy for a short period of time and often do not adhere to the antidepressants prescription, thereby having a high risk of relapse (Geddes et al., 2003). Research evidence on patients' preferences has shown that many of those who experience depression prefer psychotherapy to antidepressants (McHugh et al., 2013). Moreover, it has long been claimed that psychotherapy teaches skills to patients that they can use after the end of treatment to prevent relapse (Cuijpers, Steven D Hollon, et al., 2013). The present thesis demonstrated that psychotherapy alone or in combination with antidepressants results in enduring effects (Chapter 2 & 3). More specifically, the gains of acute psychotherapy are maintained over the long-term, suggesting that psychotherapy should be more widely accessible in primary and secondary mental health care than it is at the moment (Chapter 2). Moreover, combined treatment can also be considered as a valuable therapeutic option for the long-term management of major depressive disorder as it results in superior effects to those of antidepressants and in similar effects to those of psychotherapy (Chapter 3).

Psychotherapy is at least as effective in non-Western countries

Many adults with depression remain untreated in low- and middle-income countries mostly due to mental-health resources scarcity (Chisholm et al., 2016). From those following treatment, the majority receive antidepressants. Psychotherapy is offered to a lesser degree, although its effects are comparable to the effects of antidepressants and probably last longer (Cuijpers, Hollon, et al., 2013; Cuijpers, Sijbrandij, et al., 2013). This thesis suggested that psychological

treatments developed in Western countries are probably at least as effective in non-Western countries and thus, can be used regardless the income of the country and the geographical region (Chapter 4).

The cost-effectiveness of depression treatment has limited evidence base

The clinical effectiveness of several forms of therapy (e.g. psychotherapy, pharmacotherapy) in treating major depression is well known. However, relatively less is known about the cost-effectiveness of the main existing treatments for major depression. CBT, the most extensively examined intervention, seems cost-effective compared to antidepressants over the long-term. However, combined treatment presented conflicting cost-outcomes across the included trials, suggesting that its cost-effectiveness is still unclear. Moreover, very limited economic data were found for different types of psychotherapy and different classes of antidepressants. Overall, this thesis highlighted that there are significant gaps in economic evidence on the clinical management of major depression (Chapter 5).

Both guided and unguided Internet-based psychotherapy can serve as first-step treatment for depression

Innovations in health care delivery, such as self-guided Internet-based interventions, can provide treatment access at low cost to large numbers of individuals with depression worldwide. However, many health care systems remain hesitant to implement internet-based treatments. Among the barriers to implementation are concerns regarding effectiveness, treatment engagement and patients' safety.

Analyses of IPD data revealed that self-guided iCBT produces a small but significant effect in reducing depression severity and in increasing response to treatment (Chapter 6 & Chapter 7). This small effect can have a high impact when it applies in large populations (Chapter 7). Moreover, results of Chapter 9 showed that participants in self-guided iCBT were significantly less likely to deteriorate compared to participants in control conditions. None of the examined individual and study-level variables significantly influenced treatment outcomes, suggesting that most individuals with depression can use self-guided iCBT (Chapter 6 & Chapter 9). Treatment adherence predicted better depression outcomes within the intervention group since the participants who completed more treatment sessions had higher chances of symptom reduction and treatment response (Chapter 6). Analysis on predictors of dropout in self-guided Internet-based interventions showed that dropout is predicted from several variables, such as gender, age, educational background, and comorbid anxiety symptoms (Chapter 8). This knowledge will assist us in utilizing the self-guided form of Internet-based therapy in the most efficient way and in finding ways to improve treatment adherence and consequently treatment effects.

It is well documented that guided forms of Internet-based treatment are effective in reducing depression symptoms. However, important outcomes for clinical decision-making, such as remission and response, have not been addressed in any meta-analysis of Internet-based guided psychotherapy for depression (Richards & Richardson, 2012). Results of Chapter 10

indicated that the intervention led to statistically significant higher response and remission rates compared to controls at the post-treatment assessment. Furthermore, moderator analyses showed that older and native-born participants were more likely to respond and remit compared to younger participants and ethnic minorities respectively (Chapter 10). Moreover, participants with higher levels of depression symptoms at the baseline had higher chances to remit after receiving guided Internet-based psychotherapy (Chapter 10). Overall, this IPD meta-analysis showed that guided online therapy results in substantial clinically relevant changes for adults with depression. Thus, such interventions may complement existing routine treatment services (Chapter 10).

STRENGTHS AND LIMITATIONS

Among the strengths of this thesis is the systematic methods employed to summarise the existing literature evidence and provide reliable conclusions on the short and long-term outcomes of psychotherapy for depression, its costs, adherence and negative effects. Systematic reviews and meta-analyses yield more precise estimates of effect sizes, while exploring for inconsistencies across studies (Chapters 2-10). Other important strength of this thesis is the extensive evaluation of the validity of the included trials (Chapters 2-10). Moreover, the effects of Internet-based interventions have been examined based on the IPD meta-analytic approach, which is considered the gold standard in identifying predictors and moderators of treatment outcomes and dropout (Chapters 6-10). The IPD methodological approach maximizes the statistical power to yield more precise and robust estimate of the treatment effect. Regarding the included studies, all of them were RCTs, which give the highest level of evidence. Another strength of the included studies is that trials on Internet-interventions had high methodological quality. Thus, the overall risk of bias was low, which allows us to be confident that the present analyses on the effects of Internet-interventions are relatively free of critical biases (chapters 6-10).

Despite the strengths of this thesis, several limitations related to the methodological approach of systematic reviews and meta-analyses should be mentioned. Meta-analyses are dependant on the existing number of trials, for instance there was a limited number of trials comparing the results of combined treatment with psychotherapy alone (eight trials in the acute phase and one in maintenance phase; Chapter 3). Thus, conclusions on this comparison should be interpreted cautiously. Moreover, the results of a meta-analysis may in some cases be influenced by publication bias. In some of the examined comparisons there was an indication of publication bias, suggesting that studies with negative findings remained unpublished (e.g. the comparison between combined treatment versus antidepressants alone in the acute phase; Chapter 3). However, it should be noted that results remained significantly in favour of psychotherapy after adjustment for publication bias across all comparison that were suspected for publication bias. Many other bias linked to study selection may influence the results of a meta-analysis. For instance, the results of Chapter 4 on the effects of psychotherapy in non-Western countries were at risk of selection bias because the searches were limited to Western

databases. Thus, there is a possibility that studies published in other languages were not directly accessible through these databases. For some questions of interest, a meta-analysis could not be performed. More specifically, in Chapter 5 a meta-analysis could not be performed due to high heterogeneity in the cost related outcomes. Thus, an overall effect estimate could not be given. Finally, regarding the IPD methodology, the included RCTs did not report on several variables of interest (e.g., symptom duration) and thus, the effects of these variables could not be estimated (Chapters 6-10). Moreover, many of the examined predictors were not reported across all included studies. This might have resulted in reduced statistical power to predict effects for some variables of interest (Chapters 6-10).

Several other limitations related to the included studies should be acknowledged. An important limitation is the presence of statistical heterogeneity that was observed across the included RCTs (Chapters 2, 6 & 10). In some cases the heterogeneity was influenced by the presence of two outliers, which were removed from further analyses (Chapter 2). However, in many cases the examined moderators could not explain heterogeneity (Chapters 6 & 10). Moreover, a frequently used control group in the included trials was treatment as usual, which was in many cases poorly defined and varied across countries (chapters 2-6 & 9-10). Risk of bias varied in many comparisons (Chapters 2 & 3), while in Chapter 4 only a handful of trials were rated as at low risk of bias. In most of the cases risk of bias was not associated with treatment outcomes (Chapters 2 & 3). However, sub-group analyses of chapter 4 indicated that studies at low risk of bias had significantly lower effects compared to those at high risk of bias. Moreover, in some comparisons the majority of the included RCTs recruited participants through community, thereby limiting the generalizability of the present findings to clinical samples (Chapters 6-10). Finally, RCTs present several disadvantages although they are considered the gold standard of evidence-based medicine. For example, a common difficulty of the RCT design is the very limited inclusion criteria of participants (e.g., patients with suicidal ideation are often excluded from trials focusing on depression), which may have limited the generalizability of the present findings to all individuals with depression.

CLINICAL AND POLICY IMPLICATIONS

The present thesis aimed to provide the evidence base for the use of psychotherapy in the short- and the long-term treatment of adult depression. More specifically, stakeholders (e.g., clinicians, policy makers, guidelines developers and patients) can use the current findings to make treatment choices for depression. Although clinical guidelines recommend the use of psychotherapy as a first-line treatment for depression, antidepressants remain the most prescribed treatment in clinical practice worldwide (Gelenberg et al., 2010; National Collaborating Centre for Mental Health, 2010b; Parikh et al., 2009).

Currently the majority of patients with depression receive pharmacotherapy while psychotherapy and combined treatment are offered to a lesser degree. The results of Chapter 3 demonstrated that combined psychotherapy with pharmacotherapy has better long-term

outcomes compared to monotherapy with antidepressants. Thus, in light of the enduring effects combined therapy may be preferred to monotherapy with antidepressants both in the acute and maintenance treatment phase. Moreover, the present thesis showed that acute psychotherapy results in better outcomes compared to controls (Chapter 2) as well as in similar effects to those of combined therapy over the long-term (Chapter 3). This suggests that psychotherapy is also a valuable treatment option for the long-term management of depression. In evidence-based practice decisions should be made based on treatment effectiveness and patients' preferences. Given that many patients with depression prefer psychotherapy to antidepressants (Kathryn McHugh, Whitton, Peckham, Welge, & Otto, 2013), access to both psychotherapy and pharmacotherapy in primary and secondary mental health care may increase the chance of patients receiving their preferred treatment.

Despite the limited economic evidence of the available treatment options for depression (Chapter 5), it is clear that health care resources should be utilised in the most efficient way. Face-to-face psychotherapy is considered a resource-intensive treatment and thus, it is offered less than antidepressants in routine practice. Innovative therapeutic approaches, such as Internet-based interventions, have the potential to bridge the gap between the demand for psychotherapy and the availability of such treatment. The substantial effects of guided Internet-Interventions on remission and response rates support the use of these treatments in primary care as a first-step treatment approach for adult depression (Chapter 10). Moreover, although recent treatment guidelines recommend the use of guided Internet-based interventions in individuals with mild to moderate symptoms of depression, the present evidence supports their use in a wider group of individuals (including those with higher levels of depressive symptoms; Chapter 10). Guided online psychotherapy is less resource intensive and thus, it can help clinicians in giving face-to-face psychotherapy to those who need it most. The present thesis recommends that guided Internet-based psychotherapy should be available in routine practice along with other evidence-based treatment options and it should be offered based on patients' preferences and needs.

Self-guided forms of Internet-based psychotherapy have the potential to increase further the access and the availability of evidence-based treatment for depression. However, concerns about the effectiveness and safety of such interventions are obstacles to their application in regular care (Waller & Gilbody, 2009). This thesis demonstrated that self-guided Internet-based CBT has a small but significant effect in treating depression (Chapter 6 and 7) and leads to less symptom deterioration rates compared to controls (Chapter 9). These small effects are clinically relevant because they can have a large impact when applied to large populations. Given that psychotherapy is no less effective in non-Western countries and these effects are not associated with treatment format (Chapter 4), policy makers may consider the use of low-intensity treatment (e.g., self-help iCBT) in these countries. Thus, this thesis suggests that self-guided iCBT can be offered as first step treatment approach in countries where mental health care services are limited or inaccessible due to other reasons. Additionally, this therapy can be an alternative to watchful waiting in general practice. It should be noted that another concern

commonly reported about self-guided psychotherapy is the low treatment engagement rates observed in this type of treatment. The findings of the present thesis showed, indeed, that self-guided Internet-based psychotherapy has low adherence rates (Chapter 8). Results of Chapter 6 suggested that treatment outcomes were better for participants who presented higher adherence levels. Moreover, dropout rates are higher for different groups of individuals, such as people with comorbid anxiety symptoms (Chapter 8). Therefore, all relevant stakeholders should be aware that dropout is high and important in self-guided treatments. Further, different patient groups have a different risk of treatment dropout. This thesis suggests that patients at risk of dropout should be referred to other more appropriate treatment options.

As mentioned before, patients' preferences should be taken into account in evidence-based practice. It is therefore important to note that research on patients' preferences has shown that not all patients hold positive views of self-help treatment (Hanson, Webb, Sheeran, & Turpin, 2016; Musiat et al., 2014). These views may be reflecting a perception that self-help is less effective compared to face-to-face psychotherapy (Musiat et al., 2014). Thus, the public perception about these novel treatments should be improved before they are disseminated into clinical practice.

SUGGESTIONS FOR FUTURE RESEARCH

Besides the clinical implications discussed above, the findings of this thesis suggest several research priorities related to the examined topics.

The findings of this thesis showed that although psychotherapy has long-lasting effects, the magnitude of these effects decline over time (Chapter 2). Future studies should explore ways to enhance the durability of the effects of psychotherapy over longer follow-up periods. In this respect, continuation or maintenance psychotherapy may help in sustaining the magnitude of the treatment effect over time. In Chapter 2 firm conclusions could not be drawn regarding the long-term effects of several psychotherapeutic types (e.g., psychodynamic therapy) because few studies exist that address these types of therapy. Future studies should examine different psychotherapeutic types to allow a better understanding of the long-term effects of each type of psychotherapy separately. In Chapter 3 acute combined therapy presented similar long-term effects with those of acute psychotherapy across a small number of studies (n = 7). Moreover, only one trial examined the comparison between maintenance combined treatment and maintenance psychotherapy. Thus, conclusions regarding the relative long-term effectiveness of combined treatment versus psychotherapy were interpreted cautiously (Chapter 3). Future studies should examine the comparison between combined treatment and psychotherapy to provide more robust long-term evidence.

Treatment cost is an important barrier to the translation of the aforementioned clinical recommendations into practice. Given that health care systems face increasing budgetary pressures, the economic evaluation is crucial for health policy decision-making. Although the

availability of health economic evidence has increased over the past decades, there are still important evidence gaps regarding the cost-effectiveness of the most common treatment options for adult depression (Chapter 5). Therefore, it is unclear whether the existing treatments for depression are cost-effective. As reported by Chapter 5, there are gaps in knowledge related to which psychotherapeutic type or medication is likely to be most cost-effective. Moreover, little is known about the long-term impact on costs of the existing treatments for depression. Thus, health economic research should focus on rarely evaluated interventions (e.g., self-help interventions) and on long-term comparisons of well-studied treatments (e.g. CBT). Moreover, future studies should focus on prediction models to ensure treatments are targeted at those unlikely to experience a natural recovery.

Chapters 6 and 7 emphasised the possibility to use self-guided Internet-based CBT in low and middle countries where mental health facilities are scarce. Given that Chapter 4 reported that psychotherapy was effective in non-western countries regardless the income of the country or the treatment format, this thesis suggests that more studies are needed to examine how self-guided Internet-based CBT can be successfully disseminated and implemented in non-Western countries. Chapter 6 demonstrated that participants who adhered best to the online treatment had better outcomes than those who did not, suggesting that treatment adherence positively influences treatment outcomes. Additionally, Chapter 8 revealed several predictors of treatment dropout including age, gender, educational level and comorbidity. Thus, further research is needed to improve treatment engagement by tailoring the self-guided interventions to the needs of the identified groups at risk of dropout. In this way the positive outcomes of self-guided interventions will be maximised.

Chapters 6, 9 and 10 reported that several variables of interest could not be examined because the majority of the included studies did not assess them. Variables such as previous depression episodes or duration of symptoms may influence the strength of treatment response. For instance, duration of symptoms is important because individuals with chronic mild depressive symptoms may not respond rapidly to treatment, thereby having poor treatment outcomes. Moreover, there are some indications that number of previous episodes is related to worse treatment outcomes (Andersson, Bergström, Holländare, Ekselius, & Carlbring, 2004). Thus, the present thesis encourages future trials to measure a broader range of variables including symptom duration, number of previous episodes as well as additional moderators, such as sleep quality and cognitive performance. A wide range of potential moderators will help us to understand better who is likely to benefit from self-help Internet-based psychotherapy.

The majority of the studies included in Chapters 6-10 were recruited through community. Individuals recruited from the community seek proactively help for their symptoms and thus, differ systematically from those recruited through clinical samples. This limits substantially the generalizability of the present findings to the whole population with depression. Therefore, the present thesis highlights the need for more pragmatic RCTs focusing on the effectiveness of self-help Internet-based interventions in routine care settings. Furthermore, studies on long-

term effects of self-help Internet-based psychotherapy are largely lacking. More research is needed to examine long-term outcomes of these treatments, in particular because seek for additional help might be affected due to treatment (Christensen, Leach, Barney, Mackinnon, & Griffiths, 2006). Finally, as reported in chapter 7 there is a need for trials addressing the relative effectiveness of self-guided and guided Internet-based psychotherapy. This will allow us to investigate differential predictors of outcome for different treatment formats.

CONCLUSIONS

The present thesis aimed at improving current knowledge on the effectiveness of psychotherapy for adult depression by reviewing existing evidence on short and long-term outcomes, costs, adherence and negative effects. The present finding can be summarised as follows:

A. Combined psychotherapy with pharmacotherapy may be a valuable treatment approach for the long-term management of depression. In addition, psychotherapy alone may also be considered as treatment with long-lasting positive outcomes on both depression and quality of life. Future research should examine further the direct comparison between combined treatment and psychotherapy alone over the long-term.

B. Psychotherapeutic interventions developed in Western can be translated to non-Western countries. Moreover, the effects of psychotherapy are not influenced by the income of the country or the treatment format. This suggests that self-guided forms of psychotherapy may have great potential to increase access to treatment in non-Western countries.

C. There is limited evidence regarding the cost-effectiveness of several treatments for major depression including psychotherapy and pharmacotherapy. Future studies should explore further the economic evidence of different psychotherapeutic or medication types and examine long-term outcomes.

D. Self-guided Internet-based CBT has a small but significant effect in treating adults with depressive symptoms. Moreover, this treatment format has overall lower symptom deterioration rates compared to controls. These findings encourage the use of self-guided Internet-based CBT either as an alternative to watchful waiting in countries with well-endowed health care systems or as a first-step treatment approach in countries where mental health resources are limited or inaccessible due to other reasons.

E. Treatment adherence influences positively the outcomes of self-guided Internet-based psychotherapy. Moreover, the present thesis showed that this type of psychotherapy has low adherence rates. Nevertheless, treatment dropout can be predicted by several variables and thus, it may be prevented by tailoring the self-help interventions to the needs of the groups at risk of dropout.

F. Guided Internet-based psychotherapy leads to significantly higher remission and response rates compared to controls in adults with depressive symptoms. This finding supports the use of guided interventions as first-step treatment approach for adult depression.

To conclude, the present thesis gave substantial evidence supporting the short- and the long-term effectiveness of psychotherapy in treating adult depression. Overall, psychotherapy should be more accessible and available in primary care worldwide and it should be provided based on patients' needs and preferences. Nevertheless, the cost effectiveness of psychotherapy has limited evidence base and needs to be examined further by future research. Self-help Internet-based psychotherapy presents opportunities and challenges. The present outcomes support the use of self-help delivered via Internet as first-step treatment approach for depression.

11

SUMMARY

PART I - INTRODUCTION

CHAPTER 1

Depression is a common mental disorder characterised by low mood and diminished interest in most activities (American Psychiatric Association, 2013). It is widely recognized as a major public health problem because of its chronic nature, disability and high prevalence (Üstün et al., 2004b). Depression can be effectively treated with pharmacotherapy, psychotherapy or with the combination of psychotherapy and antidepressant medications (Cuijpers, Andersson, et al., 2011; Turner et al., 2008). Antidepressants are currently used as first-line treatment for depression, while psychotherapy is offered to a lesser degree and only a small number of patients receive combined treatment. Although effective treatments are available, not many people with depression seek help or receive treatment for their symptoms (Wang et al., 2005). Especially in low- and middle-income countries only a small number of adults with depression receive any kind of treatment (World Health Organization, 2010). Access barriers to psychotherapy include the cost of treatment, the limited availability of trained clinicians, stigma fears and patients' attitudes towards depression and treatment (Clement et al., 2015; Mohr et al., 2010; Mojtabai et al., 2011). Self-guided Internet-based treatments have the potential to overcome many psychotherapy barriers, thereby increasing its availability and accessibility (Cuijpers et al., 2017; Titov et al., 2010).

Although there is a growing body of literature on psychotherapy effectiveness, there are still many clinically relevant questions that remain unanswered. Little is known about the long-term effects of psychotherapy alone or in combination with antidepressant medications. Moreover, it is still not clear whether psychotherapeutic interventions developed in high-income countries are also effective in low- and middle-income countries. It is also unclear if psychotherapeutic interventions are cost effective. With regard to purely self-guided Internet based psychotherapy, further research is needed to give the best estimate of these interventions, to evaluate possible negative effects and to examine which factors influence the dropout rates. Regarding guided web-based interventions, very little is known about important additional clinical outcomes, such as remission and response rates. The present thesis aimed at improving current knowledge on the effectiveness of psychotherapy by reviewing existing research evidence through a series of systematic reviews and meta-analyses.

PART II – CONVENTIONAL STUDY-LEVEL SYSTEMATIC REVIEWS AND META-ANALYSES

The second part of this thesis consists of four chapters reviewing existing evidence on: a) the long-term effects of psychotherapy alone or in combination with antidepressants, b) the effects of psychotherapy in non-Western countries, and c) the cost effectiveness of treatments for major depression. In this part conventional study-level systematic reviews and meta-analyses were employed to answer the questions of interest.

CHAPTER 2

Chapter 2 describes the outcomes of a meta-analysis of 44 RCTs (6096 participants) examining the long-term effects of psychotherapy compared to controls on depression and quality of life. Results showed that psychotherapy outperformed control groups in reducing depressive symptoms (OR =1.95) and in improving quality of life (g = .22) at 6 months or longer post-randomisation. Sub-group analyses indicated that studies employing booster sessions had better depression outcomes than those that did not. These findings remained robust in sensitivity analyses where different outcomes (e.g. recovery, remission, etc.) and different psychotherapeutic types were analysed separately, with an exception of non-directive counselling, which was found to be somewhat less efficacious. Meta-regression analysis indicated that the magnitude of the effects of psychotherapy declines over longer periods of follow up. In summary, psychotherapy results in enduring effects on depression and quality of life and thus, it should be more widely available and accessible in primary care.

CHAPTER 3

Chapter 3 is a meta-analysis of 23 RCTs (2184 participants) comparing the long-term effects of combined treatment (psychotherapy with pharmacotherapy) to psychotherapy or pharmacotherapy alone in patients with major depression. In the acute phase, combined treatment resulted in better response rates compared to antidepressants (OR = 2.93). Moreover, non-significant differences were found for the comparison between combined treatment and psychotherapy. In the maintenance phase, combined treatment resulted in better-sustained response compared to antidepressants (OR = 1.61), while the comparison with psychotherapy was not possible due to limited number of trials (n = 1). These findings suggest that combined treatment is the best available treatment option for the long-term management of major depression. Psychotherapy alone can also be considered as an effective treatment option because it presents comparable long-term outcomes to those of combined treatment.

CHAPTER 4

Chapter 4 reports the results of a meta-analysis examining the effectiveness of psychotherapy in Western (n = 221 studies) and non-Western countries (n = 32) in treating adult depression. Psychotherapy resulted in large effects compared to controls in non-Western countries (g = 1.10). However, the magnitude of these effects was reduced after adjusting for publication bias (g = .73). Heterogeneity was high (I^2 = 90%) and reduced to moderate after exclusion of

outliers. Sub-group analyses showed that: a) studies at low risk of bias had significantly lower effect sizes that those at high risk of bias, b) studies comparing psychotherapy to treatment as usual had higher effects than those comparing psychotherapy to other control conditions, such as waiting lists, and c) studies conducted in non-Western countries had higher effect sizes compared to those conducted in Western countries. Meta-regression analyses indicated that studies conducted in low/lower middle and upper middle-income countries had significantly higher effect sizes than those conducted in high-income countries. The results of this meta-analysis suggested that psychological treatments developed in Western countries are probably no less effective in non-Western countries. Thus, psychotherapy can be used regardless the income of the country and the geographical region.

CHAPTER 5

Chapter 5 is a narrative systematic review of 14 RCTs examining the cost-effectiveness of main existing treatments for major depression (e.g. psychotherapy, pharmacotherapy, etc.). This study showed a wide variability in the economic evidence across the included trials. The most extensively examined psychotherapeutic intervention was CBT, which was found to be cost effective compared to antidepressants over the long-term. Moreover, the combination of psychotherapy with pharmacotherapy presented mixed economic outcomes, suggesting that the cost-effectiveness of combined treatment remains unclear. This review concluded that there are several knowledge gaps regarding the cost effectiveness of different psychotherapeutic types, treatment formats and antidepressants types. Finally, very little is known regarding the cost-effectiveness of other treatment options such as, transcranial magnetic stimulation.

PART III – INDIVIDUAL PARTICIPANT DATA META-ANALYSES

The third part of this thesis consists of five chapters examining the effectiveness, adherence and negative outcomes of self-help Internet based treatments for adult depression. A series of individual participant data (IPD) meta-analyses were conducted to examine the treatment effects as well as predictors and moderators of treatment outcome and treatment dropout.

CHAPTER 6

Chapter 6 presents the results of an IPD meta-analysis of 13 RCTs (3876 individual participant data) examining the effects of self-guided Internet-based CBT compared to controls in reduction of depressive symptoms and in treatment response (50% reduction of baseline symptoms). Results showed that self-guided CBT has superior outcomes compared to controls in both symptom reduction (g = 0.32) and treatment response (OR = 1.88; NNT = 8). None of the examined individual and study-level variables significantly influenced treatment outcomes. This suggests that most individuals with depression can use self-guided Internet-based CBT. Finally, higher treatment adherence rates predicted better depression outcomes within the intervention group. These results encourage the use of self-guided Internet-based CBT as a first-step treatment approach or as alternative to watchful waiting in clinical practice for adult depression.

CHAPTER 7

Chapter 7 is a response to concerns raised regarding the interpretation of the findings of Chapter 6. This chapter emphasizes that the overall effects of self-guided Internet based CBT are small but clinically relevant because they can have high impact in large populations. The chapter acknowledges the possibility of publication bias and that there are some indications from indirect evidence that guided interventions produce superior results compared to self-guided interventions. However, this superiority remains to be confirmed by direct comparisons between self-guided and guided Internet-based interventions.

CHAPTER 8

Chapter 8 examines predictors of treatment dropout in self-guided Internet-based psychotherapy across 10 RCTs with 2705 participants. Results indicated that male gender, individuals with low education educational background, participants with comorbid symptoms of anxiety and younger adults were at higher risk of dropout before the completion of 75% of treatment sessions. These findings suggest that dropout can be predicted and thus, may potentially be prevented by tailoring the online interventions to the needs of the identified groups at risk of dropout.

CHAPTER 9

Chapter 9 describes the results of an IPD meta-analysis of 13 RCTs (3876 participants) examining symptom deterioration of self-guided Internet-based CBT compared to controls in adults with depression. Results showed that self-guided Internet-based CBT had significantly

lower deterioration rates compared to controls at the post-treatment assessment (OR = 0.62). None of the examined individual- and study level variables was significantly associated with symptom deterioration rates. Although self-guided Internet-based results in lower rates of negative outcomes on symptoms compared to controls, 5.8% of participants experienced deterioration after the treatment. Thus, deterioration should be carefully monitored and reported by future studies.

CHAPTER 10

Chapter 10 presents the results of an IPD meta-analysis examining the effects of guided Internet-based psychotherapy compared to controls on remission and treatment response in adults with depression across 24 RCTs (4889 participants). Results showed that guided Internet-based psychotherapy leads to higher remission (OR = 2.41) and treatment response rates (OR = 2.49) compared to controls. Further, moderator analyses showed that older and native-born participants were more likely to respond and remit compared to younger participants and ethnic minorities respectively. Moreover, participants with higher levels of depression symptoms at the baseline had higher chances to remit after receiving guided Internet-based psychotherapy. This IPD meta-analysis demonstrated that guided Internet-based psychotherapy results in substantial clinically relevant changes and thus, it may complement existing routine treatment services.

PART IV – GENERAL DISCUSSION

CHAPTER 11

Chapter 11 summarises the main findings of this thesis and presents the main strengths and limitations. Moreover, it provides suggestions for clinical practice and future research. This thesis aimed at improving current knowledge on the effectiveness of psychotherapy by reviewing existing research evidence though a series of systematic reviews and meta-analyses. Overall, results showed that psychotherapy alone or combined with antidepressant leads to enduring treatment effects on depression. Moreover, psychotherapy is no less effective in non-Western countries. Despite the ample evidence on clinical effectiveness, there is limited evidence regarding the cost-effectiveness of several treatments for major depression including psychotherapy. Self-guided Internet-based psychotherapy presents opportunities and challenges. The outcomes of this thesis support the use of self-help as a first-step treatment approach for adult depression. However, several limitations of self-help Internet-based psychotherapy should be addressed before it can be disseminated into routine practice.

SAMENVATTING

DEEL I – INTRODUCTIE

HOOFDSTUK 1

Depressie is een veelvoorkomende psychische stoornis die gekenmerkt wordt door lage stemming en verminderde interesse in de meeste activiteiten (American Psychiatric Association, 2013). Het wordt beschouwd als een groot probleem voor de volksgezondheid vanwege de chronische aard, impact op welzijn en hoge prevalentie (Üstün et al., 2004b). Depressie kan effectief behandeld worden met farmacotherapie, psychotherapie, of de combinatie hiervan (Cuijpers, Andersson, et al., 2011; Turner et al., 2008). Antidepressiva worden momenteel voorgeschreven als eerstelijnsbehandeling voor depressie, terwijl psychotherapie in mindere mate wordt aangeboden. Slechts een klein deel van de patiënten krijgt een gecombineerde behandeling van psychotherapie en farmacotherapie. Hoewel effectieve behandelingen beschikbaar zijn, zoeken weinig depressieve mensen hulp en worden er weinig behandeld voor hun klachten (Wang et al., 2005). Vooral in lage-inkomenslanden en middeninkomenslanden krijgt slechts een klein aantal van de volwassenen met depressie een behandeling (World Health Organization, 2010). Bekende drempels voor het krijgen van psychotherapie zijn de kosten van een behandeling, angst voor stigma en patiëntenattitudes jegens depressie en behandeling (Clement et al., 2015; Mohr et al., 2010; Mojtabai et al., 2011). Zelfhulpbehandelingen via het internet hebben het potentieel om deze drempels te verlagen en de beschikbaarheid en toegankelijkheid van psychotherapie te verbeteren (Cuijpers et al., 2017; Titov et al., 2010).

Ondanks de toenemende hoeveelheid literatuur over de effectiviteit van psychotherapie, blijven veel klinisch relevante vragen nog onbeantwoord. Er is weinig bekend over de langetermijneffecten van psychotherapie, zowel met als zonder antidepressiva. Tevens is het nog niet duidelijk of psychotherapeutische interventies die ontwikkeld zijn in hoge-inkomenslanden ook effectief zijn in lage-inkomenslanden of middeninkomenslanden. Het is ook niet duidelijk of psychotherapeutische interventies kosteneffectief zijn. Betreft online zelfhulpbehandelingen zonder begeleiding is meer onderzoek nodig om mogelijke negatieve effecten te evalueren en te onderzoeken welke factoren van invloed zijn op het percentage uitvallers. Betreft online behandelingen met begeleiding is nog weinig bekend over belangrijke additionele uitkomsten, zoals de respons/remissie ratio. De huidige these beoogt bij te dragen aan de bestaande kennis over de effectiviteit van psychotherapie door een overzicht te geven van bestaand onderzoek door middel van een serie systematische reviews en meta-analyses.

DEEL II – CONVENTIONELE SYSTEMATISCHE REVIEWS EN META-ANALYSES OP STUDIE NIVEAU

Het tweede deel van deze these bestaat uit 4 hoofdstukken die de bestaande evidentie reviewen betreft: a) de langetermijneffecten van psychotherapie, zowel op zichzelf staand als gecombineerd met antidepressiva, b) de effecten van psychotherapie in niet-westerse landen, en c) de kosteneffectiviteit van behandelingen voor depressieve stoornis. In dit deel worden de onderzoeksvragen beantwoord door middel van conventionele systematische reviews en meta-analyses.

HOOFDSTUK 2

Hoofdstuk 2 beschrijft de uitkomsten van een meta-analyse van 44 randomised controlled trials (RCT's; 6096 deelnemers) waarin de langetermijneffecten van psychotherapie op depressie en kwaliteit van leven is onderzocht in vergelijking met controle condities. De resultaten toonden aan dat psychotherapie depressieve symptomen vermindert (odds ratio [OR] = 1.95) en kwaliteit van leven verbetert (g = 0.22) ten opzichte van controle condities, berekend 6 maanden of langer na randomisatie. Subgroep analyses wezen uit dat interventies met booster sessies betere uitkomsten hadden dan interventies zonder booster sessies. Deze resultaten bleven robuust in gevoeligheidsanalyses waarin verschillende uitkomsten (bijv. herstel, remissie, etc.) en verschillende types psychotherapie apart geanalyseerd werden, met uitzondering van non-directieve begeleiding, wat iets minder effectief was. Meta-regressieanalyse wees uit dat de effectgrootte van psychotherapie na langere tijd afneemt. Samengevat resulteert psychotherapie in blijvende effecten op depressie en kwaliteit van leven en zou dus breder beschikbaar en toegankelijker moeten zijn in de eerstelijns zorg.

HOOFDSTUK 3

Hoofdstuk 3 is een meta-analyse van 23 RCTs (2184 deelnemers) waarin de langetermijneffecten van gecombineerde therapie (psychotherapie en farmacotherapie) wordt vergeleken met die van psychotherapie of farmacotherapie bij patiënten met depressieve stoornis. In de acute fase resulteerde gecombineerde therapie in een hoger responspercentage dan antidepressiva (OR = 2.93). De vergelijking tussen gecombineerde behandeling en psychotherapie leverde daarnaast geen significante verschillen op. In de onderhoudsfase resulteerde gecombineerde behandeling in betere respons vergeleken met antidepressiva (OR = 1.61), terwijl de vergelijking met psychotherapie niet mogelijk was vanwege een te klein aantal studies (n = 1). Deze bevindingen suggereren dat gecombineerde therapie de beste beschikbare optie is voor de langetermijnbehandeling van depressieve stoornis. Psychotherapie alleen kan ook beschouwd worden als een effectieve behandeloptie, omdat de langetermijnuitkomsten vergelijkbaar zijn met die van gecombineerde therapie.

HOOFDSTUK 4

In hoofdstuk 4 worden de resultaten gerapporteerd van een meta-analyse van de effectiviteit van psychotherapie voor depressie in westerse (n = 221 studies) en niet-westerse (n = 32)

landen. Psychotherapie had grote effecten vergeleken met controle condities in niet-westerse landen (g = 1.10). De grootte van de effecten werd echter verkleind na te corrigeren voor publicatiebias (g = .73). De heterogeniteit was hoog (I2 = 90%) en werd gereduceerd tot matig na het excluderen van uitschieters. Subgroep analyses lieten zien dat: a) studies met laag risico op bias significant lagere effectgroottes hadden dan studies met hoog risico op bias; b) studies die psychotherapie vergeleken met gebruikelijke zorg grotere effecten hadden dan studies die psychotherapie vergeleken met andere controle condities, zoals wachtlijsten; en c) studies die uitgevoerd werden in niet-westerse landen grotere effectgroottes hadden dan studies uit westerse landen. Meta-regressie analyses lieten zien dat studies die uitgevoerd waren in lage-inkomenslanden, lager-middeninkomenslanden en hoger- middeninkomenslanden significant grotere effectgroottes hadden dan studies die uitgevoerd waren in hoge-inkomenslanden. Uit de resultaten van deze meta-analyse blijkt dat psychologische behandelingen die ontwikkeld werden in westerse landen waarschijnlijk niet minder effectief zijn in niet-westerse landen. Psychotherapie kan dus ingezet worden onafhankelijk van het inkomen van een land en de geografische regio.

HOOFDSTUK 5

Hoofdstuk 5 is een narratieve systematische review van 14 RCT's die de kosteneffectiviteit van de voornaamste behandelingen van depressieve stoornis (bijvoorbeeld psychotherapie, farmacotherapie, etc.) onderzoekt. Deze studie laat een grote variatie zien in het economische bewijs van de geïncludeerde trials. De uitvoerigst onderzochte psychotherapeutische interventie was cognitieve gedragstherapie (CGT), welke op de lange termijn kosteneffectief bleek ten opzichte van antidepressiva. De combinatie van psychotherapie en farmacotherapie liet gemengde economische uitkomsten zien, waaruit blijkt dat de kosteneffectiviteit van gecombineerde behandelingen onduidelijk blijft. Deze review concludeert dat er kennis ontbreekt betreft de kosteneffectiviteit van verschillende types psychotherapie, formats van behandelingen en types antidepressiva. Tenslotte is er erg weinig bekend over de kosteneffectiviteit van andere behandelopties, zoals transcraniale magnetische stimulatie.

DEEL III – INDIVIDUELE-PATIËNTENDATA META-ANALYSES

Het derde deel van dit proefschrift bestaat uit vijf hoofdstukken die de effectiviteit, therapietrouw en negatieve uitkomsten onderzoeken van online zelfhulpinterventies voor volwassenen met depressieve stoornis. Een serie individuele-patiëntendata (IPD) meta-analyses is uitgevoerd om de effecten van de behandelingen te onderzoeken, alsmede de voorspellers en moderatoren voor behandeluitkomsten en drop-out uit de behandeling.

HOOFDSTUK 6

In hoofdstuk 6 worden de resultaten gepresenteerd van een IPD meta-analyse van 13 RCT's (3876 patiënten) die de effecten onderzoekt van onbegeleide online CGT ten opzichte van controle condities. De uitkomstmaten waren afname van depressieve symptomen en behandeling respons (een afname van 50% van symptomen ten opzichte van de voormeting). De resultaten lieten zien dat onbegeleide CGT superieure uitkomsten had vergeleken met controle condities op zowel symptoomafname (g = 0.32) als behandeling respons (OR = 1.88; number needed to treat = 8). Geen van de onderzochte variabelen op individueel niveau of studie niveau hadden een significante invloed op de uitkomsten van de behandeling. Hieruit blijkt dat de meeste depressieve individuen onbegeleide online CGT kunnen gebruiken. Tenslotte voorspelde hogere therapietrouw betere depressie uitkomsten in de interventiegroep. Deze resultaten moedigen het gebruik van onbegeleide online CGT aan als een eerste stap in de behandeling van depressie of als alternatief voor 'watchful waiting' in de klinische praktijk.

HOOFDSTUK 7

Hoofdstuk 7 is een antwoord op bezorgdheid over de interpretatie van de bevindingen van hoofdstuk 6. In hoofdstuk 7 wordt benadrukt dat de algehele effecten van onbegeleide online CGT klein zijn, maar wel klinisch relevant, omdat ze grote impact kunnen hebben in grote populaties. In dit hoofdstuk wordt de mogelijkheid tot publicatiebias erkend alsmede enkele indicaties van indirect bewijs dat begeleide interventies via het internet superieure resultaten hebben ten opzichte van onbegeleide zelfhulpinterventies via het internet. Deze superioriteit moet echter nog bevestigd worden door directe vergelijkingen tussen begeleide en onbegeleide online interventies.

HOOFDSTUK 8

In hoofdstuk 8 worden voorspellers voor uitval uit onbegeleide online psychotherapie onderzocht op basis van 10 RCT's met 2705 deelnemers. Resultaten lieten zien dat mannen, lager opgeleiden, deelnemers met comorbide angstsymptomen en jongvolwassenen een hoger risico op uitval hadden voordat 75% van de behandeling was afgemaakt. Deze bevindingen suggereren dat uitval voorspeld kan worden en, zodoende, potentieel voorkomen kan worden door online behandelingen af te stemmen op de behoeften van de geïdentificeerde groepen.

HOOFDSTUK 9

Hoofdstuk 9 beschrijft de resultaten van een IPD meta-analyse van 13 RCT's (3876 deelnemers), waarmee verslechtering van symptomen onderzocht is onder depressieve volwassenen die onbegeleide online CGT volgden of aan controle condities toegewezen waren. De resultaten lieten zien dat onbegeleide online CGT tot significant minder verslechtering leidde vergeleken met controle condities op de nameting (OR = 0.62). Geen van de onderzochte variabelen op individueel of studie niveau hingen significant samen met verslechtering van symptomen. Hoewel onbegeleide online behandeling resulteerde in minder negatieve uitkomsten vergeleken met controle condities, ervaarde toch 5.8% van de deelnemers verslechtering van symptomen na de behandeling. Verslechtering zou zodoende zorgvuldig gemonitord en gerapporteerd moeten worden door toekomstig onderzoek.

HOOFDSTUK 10

In hoofdstuk 10 worden de resultaten gepresenteerd van een IPD meta-analyse die de effecten van begeleide online psychotherapie voor depressieve volwassenen vergelijkt met controle condities (24 RCT's, 4889 deelnemers), waarbij respons op de behandeling als uitkomstmaat wordt gehanteerd. Resultaten lieten zien dat begeleide online psychotherapie leidde tot hogere remissie (OR = 2.41) en hogere respons op de behandeling (OR = 2.49) vergeleken met controle condities. Moderatoranalyses lieten verder zien dat oudere en autochtone deelnemers hogere kans op respons of remissie hadden vergeleken met (respectievelijk) jongere deelnemers en etnische minderheden. Bovendien hadden deelnemers met ernstigere depressiesymptomen op de voormeting hogere kans op remissie na het volgen van begeleide online psychotherapie. Deze IPD meta-analyse laat zien dat begeleide online psychotherapie resulteert in substantiële klinisch relevante veranderingen en zou dus een toevoeging kunnen zijn aan bestaande behandelvormen.

DEEL IV - ALGEMENE DISCUSSIE

HOOFDSTUK 11

Hoofdstuk 11 vat de belangrijkste bevindingen van deze these samen en beschrijft de voornaamste pluspunten en beperkingen. Er worden ook suggesties gegeven voor de klinische praktijk en toekomstig onderzoek. Deze these beoogde bij te dragen aan de bestaande kennis over de effectiviteit van psychotherapie door een overzicht te geven van bestaand onderzoek door middel van een serie systematische reviews en meta-analyses. Over het algemeen laten resultaten zien dat psychotherapie op zichzelf of gecombineerd met antidepressiva leidt tot langdurige effecten op depressie. Psychotherapie is bovendien niet minder effectief in niet-westerse landen. Ondanks overvloedig bewijs voor klinische effectiviteit, is er beperkt bewijs betreft de kosteneffectiviteit van meerdere behandelingen van depressieve stoornis inclusief psychotherapie. Onbegeleide online psychotherapie biedt kansen en uitdagingen. De uitkomsten van deze these onderbouwen de inzet van zelfhulp als een eerste-stap benadering voor de behandeling van depressie onder volwassenen. Er zal echter aandacht moeten worden gegeven aan verschillende beperkingen van online zelfhulptherapie voordat deze vorm van therapie breder aangeboden kan worden in de dagelijkse klinische praktijk.

REFERENCES

Abo-Zaid, G., Guo, B., Deeks, J. J., Debray, T. P., Steyerberg, E. W., Moons, K. G., & Riley, R. D. (2013). Individual participant data meta-analyses should not ignore clustering. *Journal of clinical epidemiology*, *66*(8), 865-873. e864.

Akechi, T., Okuyama, T., Onishi, J., Morita, T., & Furukawa Toshi, A. (2008). Psychotherapy for depression among incurable cancer patients. *Cochrane Database of Systematic Reviews*, (2).

Alladin, A. (2007). Handbook of cognitive hypnotherapy for depression: An evidence-based approach: Lippincott Williams & Wilkins.

Allart-van Dam, E., Hosman, C. M., Hoogduin, C. A., & Schaap, C. (2007). Prevention of depression in subclinically depressed adults: follow-up effects on the 'Coping with Depression'course. *Journal of Affective Disorders*, *97*(1), 219-228.

Alonso, J., Angermeyer, M. C., Bernert, S., Bruffaerts, R., Brugha, T., Bryson, H., . . . Gasquet, I. (2004a). Use of mental health services in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta psychiatrica scandinavica*, *109*(s420), 47-54.

Alonso, J., Angermeyer, M. C., Bernert, S., Bruffaerts, R., Brugha, T. S., Bryson, H., . . . Gasquet, I. (2004b). Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta psychiatrica scandinavica*, *109*(s420), 21-27.

Alonso, J., Petukhova, M., Vilagut, G., Chatterji, S., Heeringa, S., Üstün, T. B., . . . Bromet, E. (2011). Days out of role due to common physical and mental conditions: results from the WHO World Mental Health surveys. *Molecular psychiatry*, *16*(12), 1234.

American Psychiatric Association. (2000). Practice guideline for the treatment of patients with major depressive disorder (revision). *American Journal of Psychiatry*, *157*, 1-45.

American Psychiatric Association. (2013). Depressive Disorders *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.). Washington, DC. American Psychiatric Association.

Anderson, I., Ferrier, I., Baldwin, R., Cowen, P., Howard, L., Lewis, G., . . . Scott, J. (2008). Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2000 British Association for Psychopharmacology guidelines. *Journal of Psychopharmacology*, *22*(4), 343-396.

Andersson, G., & Cuijpers, P. (2009). Internet-based and other computerized psychological treatments for adult depression: a meta-analysis. *Cognitive Behavioral Therapy*, *38*(4), 196-205.

Andersson, G., & Titov, N. (2014). Advantages and limitations of Internet-based interventions for common mental disorders. *World Psychiatry*, *13*(1), 4-11.

Andersson, G., Bergström, J., Holländare, F., Carlbring, P., Kaldo, V., & Ekselius, L. (2005). Internet-based self-help for depression: Randomised controlled trial. *British Journal of Psychiatry*, *187*(5), 456-461.

Andersson, G., Bergström, J., Holländare, F., Carlbring, P., Kaldo, V., & Ekselius, L. (2005). Internet-based self-help for depression: randomised controlled trial. *The British Journal of Psychiatry*, *187*(5), 456-461.

Andersson, G., Bergström, J., Holländare, F., Ekselius, L., & Carlbring, P. (2004). Delivering cognitive behavioural therapy for mild to moderate depression via the Internet: predicting outcome at 6-month follow-up. *Verhaltenstherapie*, *14*(3), 185-189.

Andersson, G., Cuijpers, P., Carlbring, P., Riper, H., & Hedman, E. (2014a). Guided Internet-based vs. face-to-face cognitive behavior therapy for psychiatric and somatic disorders: a systematic review and meta-analysis. *World Psychiatry*, *13*(3), 288-295.

Andrade, L. H., Alonso, J., Mneimneh, Z., Wells, J., Al-Hamzawi, A., Borges, G., . . . De Graaf, R. (2014). Barriers to mental health treatment: results from the WHO World Mental Health surveys. *Psychological medicine*, *44*(06), 1303-1317.

Andrade, L., CaraveoβAnduaga, J. J., Berglund, P., Bijl, R. V., Graaf, R. D., Vollebergh, W., . . . Kessler, R. C. (2003). The epidemiology of major depressive episodes: results from the International Consortium of Psychiatric Epidemiology (ICPE) Surveys. *International journal of methods in psychiatric research*, *12*(1), 3-21.

Andrews, G., Cuijpers, P., Craske, M. G., McEvoy, P., & Titov, N. (2010). Computer therapy for the anxiety and depressive disorders is effective, acceptable and practical health care: a meta-analysis. *PLoS One*, *5*(10), e13196.

Andrews, G., Henderson, S., & Hall, W. (2001). Prevalence, comorbidity, disability and service utilisation Overview of the Australian National Mental Health Survey. *The British Journal of Psychiatry*, *178*(2), 145-153.

Babwah, F., Baksh, S., Blake, L., Cupid-Thuesday, J., Hosein, I., Sookhai, A., ... & Hutchinson, G. (2006). The role of gender in compliance and attendance at an outpatient clinic for type 2 diabetes mellitus in Trinidad. *Revista panamericana de salud pública*, *19*(2), 79-84.

Barber, J. P., Muran, J. C., McCarthy, K. S., & Keefe, R. (2013). Barber, JP, Muran, JC, McCarthy, KS, Keefe, RJ (2013). Research on Psychodynamic Therapies. In MJ Lambert (Ed.). Bergin and Garfield's Handbook of Psychotherapy and Behavior Change (pp. 443-494). New-York, NY: John Wiley & Sons, Inc *Bergin and Garfield's handbook of psychotherapy and behavior change* (pp. 443-494).

Barney, L. J., Griffiths, K. M., Christensen, H., & Jorm, A. F. (2009). Exploring the nature of stigmatising beliefs about depression and help-seeking: implications for reducing stigma. *BMC Public Health*, *9*, 61.

Barth, J., Munder, T., Gerger, H., Nüesch, E., Trelle, S., Znoj, H., ... & Cuijpers, P. (2013). Comparative efficacy of seven psychotherapeutic interventions for patients with depression: a network meta-analysis. *PLoS medicine*, *10*(5), e1001454.

Bass, J., Neugebauer, R., Clougherty, K. F., Verdeli, H., Wickramaratne, P., Ndogoni, L., . . . Bolton, P. (2006). Group interpersonal psychotherapy for depression in rural Uganda: 6-month outcomes. *The British Journal of Psychiatry*, *188*(6), 567-573.

Baumeister, H., Nowoczin, L., Lin, J., Seifferth, H., Seufert, J., Laubner, K., & Ebert, D. (2014). Impact of an acceptance facilitating intervention on diabetes patients' acceptance of Internet-based interventions for depression: a randomized controlled trial. *Diabetes research and clinical practice*, *105*(1), 30-39.

Baumeister, H., Reichler, L., Munzinger, M., & Lin, J. (2014). The impact of guidance on Internet-based mental health interventions—A systematic review. *Internet Interventions*, *1*(4), 205-215.

Bech, P., Lönn, S. L., & Overø, K. F. (2010). Relapse prevention and residual symptoms: a closer analysis of placebo-controlled continuation studies with escitalopram in major depressive disorder, generalized anxiety disorder, social anxiety disorder, and obsessive-compulsive disorder. *The Journal of clinical psychiatry*, *71*(2), 121-129.

Beck, A. T., & Steer, R. A. (1984). Internal consistencies of the original and revised Beck Depression Inventory. *Journal of clinical psychology*, *40*(6), 1365-1367.

Beck, A. T., Hollon, S. D., Young, J. E., Bedrosian, R. C., & Budenz, D. (1985). Treatment of depression with cognitive therapy and amitriptyline. *Archives of general psychiatry*, *42*(2), 142-148.

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). Beck depression inventory-II. *San Antonio, 78*(2), 490-498.

Beck, A. T., Steer, R. A., & Carbin, M. G. (1988). Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. *Clinical psychology review, 8*(1), 77-100.

Beck, A. T., Ward, C., & Mendelson, M. (1961). Beck depression inventory (BDI). *Archives of general psychiatry, 4*(6), 561-571.

Beck, A., Steer, R., & Brown, G. (1996). BDI-II, Beck depression inventory: manual: Psychological Corp. *San Antonio, TX*.

Beck, A.T., Hollon, S.D., Young, J.E., Bedrosian, R.C., Budenz, D. Treatment of depression with cognitive therapy and amitriptyline. *Arch Gen Psychiatry* **42**, 1985, 142-148.

Beeber, L. S., HolditchβDavis, D., Perreira, K., A Schwartz, T., Lewis, V., Blanchard, H., ... & Goldman, B. D. (2010). Shortβterm inβhome intervention reduces depressive symptoms in Early Head Start Latina mothers of infants and toddlers. *Research in nursing & health, 33*(1), 60-76.

Bellino, S., Zizza, M., Rinaldi, C., & Bogetto, F. (2006). Combined treatment of major depression in patients with borderline personality disorder: a comparison with pharmacotherapy. *Canedian journal of psychiatry, 51*(7), 453-460.

Beltman, M. W., Voshaar, R. C. O., & Speckens, A. E. (2010). Cognitive–behavioural therapy for depression in people with a somatic disease: Meta-analysis of randomised controlled trials. *The British journal of psychiatry, 197*(1), 11-19.

Berger, T., Caspar, F., Richardson, R., Kneubuhler, B., Sutter, D., & Andersson, G. (2011). Internet-based treatment of social phobia: a randomized controlled trial comparing unguided with two types of guided self-help. *Behavioral research therapy, 49*(3), 158-169.

Berger, T., Hämmerli, K., Gubser, N., Andersson, G., & Caspar, F. (2011). Internet-based treatment of depression: A randomized controlled trial comparing guided with unguided self-help. *Cognitive Behaviour Therapy, 40*(4), 251-266.

Berto, P., D'Ilario, D., Ruffo, P., Virgilio, R. D., & Rizzo, F. (2000). Depression: costβofβillness studies in the international literature, a review. *The journal of mental health policy and economics, 3*(1), 3-10.

Biesheuvel-Leliefeld, K. E., Kok, G. D., Bockting, C. L., Cuijpers, P., Hollon, S. D., van Marwijk, H. W., & Smit, F. (2015). Effectiveness of psychological interventions in preventing recurrence of depressive disorder: Meta-analysis and meta-regression. *Journal of affecive disorders, 174*, 400-410.

Blackburn, I. M., Eunson, K. M., & Bishop, S. (1986). A two-year naturalistic follow-up of depressed patients treated with cognitive therapy, pharmacotherapy and a combination of both. *Journal of affective disorders, 10*(1), 67-75.

Bloom, D., Cafiero, E., Jané-Llopis, E., Abrahams-Gessel, S., Bloom, L., Fathima, S., ... & O'Farrell, D. (2012). *The global economic burden of noncommunicable diseases*. Program on the Global Demography of Aging.

Bolton, P., Bass, J., Neugebauer, R., Verdeli, H., Clougherty, K. F., & Wickramaratne, P. (2003). Group interpersonal psychotherapy for depression in rural Uganda: a randomized controlled trial. *JAMA, 289*.

Borenstein, M., Hedges, L. V., Higgins, J. P. T., & Rothstein, H. R. (2009). *Introduction to Meta- Analysis*. Chichester, UK: Wiley.

Bosmans, J. E., Brook, O. H., Hout, H. P., Bruijne, M. C., Nieuwenhuyse, H., Bouter, L. M., . . . Tulder, M. W. (2007). Cost effectiveness of a pharmacy-based coaching programme to improve adherence to antidepressants. *Pharmacoeconomics*, *25*(1), 25-37.

Bosmans, J. E., van Schaik, D. J., Heymans, M. W., van Marwijk, H. W., van Hout, H. P., & de Bruijne, M. C. (2007). Cost-effectiveness of interpersonal psychotherapy for elderly primary care patients with major depression. *Int J Technol Assess Health Care*, *23*(4), 480-487.

Bower, P., Kontopantelis, E., Sutton, A., Kendrick, T., Richards, D. A., Gilbody, S., . . . Christensen, H. (2013). Influence of initial severity of depression on effectiveness of low intensity interventions: meta-analysis of individual patient data. *BMJ*, *346*.

Bower, P., Kontopantelis, E., Sutton, A., Kendrick, T., Richards, D. A., Gilbody, S., . . . Liu, E. T. (2013). Influence of initial severity of depression on effectiveness of low intensity interventions: meta-analysis of individual patient data. *BMJ*, *346*, f540.

Bromet, E., Andrade, L. H., Hwang, I., Sampson, N. A., Alonso, J., De Girolamo, G., . . . Iwata, N. (2011). Cross-national epidemiology of DSM-IV major depressive episode. *BMC medicine*, *9*(1), 90.

Brookes, S. T., Whitely, E., Egger, M., Smith, G. D., Mulheran, P. A., & Peters, T. J. (2004). Subgroup analyses in randomized trials: risks of subgroup-specific analyses;: power and sample size for the interaction test. *Journal of clinical epidemiology*, *57*(3), 229-236.

Bruffaerts, R., Vilagut, G., Demyttenaere, K., Alonso, J., AlHamzawi, A., Andrade, L. H., . . . De Girolamo, G. (2012). Role of common mental and physical disorders in partial disability around the world. *The British Journal of Psychiatry*, bjp. bp. 111.097519.

Bunney, W., Kleinman, A., Pellmar, T., & Goldsmith, S. (2002). Reducing suicide: A national imperative: National Academies Press.

Buntrock, C., Ebert, D., Lehr, D., Riper, H., Smit, F., Cuijpers, P., & Berking, M. (2015). Effectiveness of a web-based cognitive behavioural intervention for subthreshold depression: Pragmatic randomised controlled trial. *Psychotherapy and psychosomatics*, *84*(6), 348-358.

Burke, D. L., Ensor, J., & Riley, R. D. (2017). Metaβanalysis using individual participant data: oneβstage and twoβstage approaches, and why they may differ. *Statistics in medicine*, *36*(5), 855-875.

Burns, A., O'Mahen, H., Baxter, H., Bennert, K., Wiles, N., Ramchandani, P., . . . Evans, J. (2013). A pilot randomised controlled trial of cognitive behavioural therapy for antenatal depression. *BMC Psychiatry*, *13*(1), 1-12.

Byford, S., Barrett, B., Roberts, C., Wilkinson, P., Dubicka, B., Kelvin, R. G., . . . Goodyer, I. (2007). Cost-effectiveness of selective serotonin reuptake inhibitors and routine specialist care with and without cognitive behavioural therapy in adolescents with major depression. *British journal of psychiatry*, *191*, 521-527.

C Lee, J., M Blumberger, D., B Fitzgerald, P., J Daskalakis, Z., & J Levinson, A. (2012). The role of transcranial magnetic stimulation in treatment-resistant depression: a review. *Current pharmaceutical design*, *18*(36), 5846-5852.

Carlbring, P., Hagglund, M., Luthstrom, A., Dahlin, M., Kadowaki, A., Vernmark, K., & Andersson, G. (2013). Internet-based behavioral activation and acceptance-based treatment for depression: A randomized controlled trial. *Journal of affective disorders*, *148*(2-3), 331-337.

Carvalho, J. P., & Hopko, D. R. (2011). Behavioral theory of depression: Reinforcement as a mediating variable between avoidance and depression. *Journal of behavior therapy and experimental psychiatry*, *42*(2), 154-162.

Casacalenda, N., Perry, J. C., & Looper, K. (2002). Remission in major depressive disorder: a comparison of pharmacotherapy, psychotherapy, and control conditions. *American journal of psychiatry*, *159*(8), 1354-1360.

Chan, A. S., Wong, Q. Y., Sze, S. L., Kwong, P. P., Han, Y. M., & Cheung, M. C. (2012). A Chinese Chan-based mind-body intervention for patients with depression. *Journal of affective disorders*, *142*(1-3), 283-289.

Chan, M. F., Ng, S. E., Tien, A., Ho, M., Roger, C., & Thayala, J. (2013). A randomised controlled study to explore the effect of life story review on depression in older Chinese in Singapore. *Health Soc Care Community*, *21*(5), 545-553.

Chen, C. H., Tseng, Y. F., Chou, F. H., & Wang, S. Y. (2000). Effects of support group intervention in postnatally distressed women. A controlled study in Taiwan. *J psychosomatics research*, *49*(6), 395-399.

Chiang, K. J., Chen, T. H., Hsieh, H. T., Tsai, J. C., Ou, K. L., & Chou, K. R. (2015). One-year follow-up of the effectiveness of cognitive behavioral group therapy for patients' depression: A randomized, single-blinded, controlled study. *Scientific world journal, 2015*, Article ID 373149.

Chisholm, D., Sweeny, K., Sheehan, P., Rasmussen, B., Smit, F., Cuijpers, P., & Saxena, S. (2016). Scaling-up treatment of depression and anxiety: a global return on investment analysis. *The Lancet Psychiatry*, *3*(5), 415-424.

Cho, H. J., Kwon, J. H., & Lee, J. J. (2008). Antenatal cognitive-behavioral therapy for prevention of postpartum depression: a pilot study. *Yonsei medical journal*, *49*(4), 553-562.

Choi, I., Zou, J., Titov, N., Dear, B. F., Li, S., Johnston, L., . . . Hunt, C. (2012). Culturally attuned Internet treatment for depression amongst Chinese Australians: a randomised controlled trial. *Journal of affecive disorders, 136*(3), 459-468.

Choi, N. G., Sirey, J. A., & Bruce, M. L. (2013). Depression in homebound older adults: recent advances in screening and psychosocial interventions. *Current translational geriatrics and experimental gerontology reports*, *2*(1), 16-23.

Christensen, H., Griffiths, K. M., & Farrer, L. (2009). Adherence in internet interventions for anxiety and depression. *Journal of medical internet research, 11*(2), e13.

Christensen, H., Griffiths, K. M., & Farrer, L. (2009). Adherence in internet interventions for anxiety and depression: systematic review. *Journal of medical Internet research*, *11*(2).

Christensen, H., Griffiths, K. M., & Jorm, A. F. (2004). Delivering interventions for depression by using the internet: randomised controlled trial. *Bmj, 328*(7434), 265.

Christensen, H., Leach, L. S., Barney, L., Mackinnon, A. J., & Griffiths, K. M. (2006). The effect of web based depression interventions on self reported help seeking: randomised controlled trial [ISRCTN77824516]. *BMC Psychiatry*, *6*, 13-13.

Clarke, G., Eubanks, D., Reid, C. K., O'Connor, E., DeBar, L. L., Lynch, F., ... & Gullion, C. (2005). Overcoming Depression on the Internet (ODIN)(2): a randomized trial of a self-help depression skills program with reminders. *Journal of medical Internet research*, *7*(2).

Clarke, G., Kelleher, C., Hornbrook, M., DeBar, L., Dickerson, J., & Gullion, C. (2009). Randomized effectiveness trial of an Internet, pure self-help, cognitive behavioral intervention for depressive symptoms in young adults. *Cognitive behaviour therapy*, *38*(4), 222-234.

Clarke, G., Reid, E., Eubanks, D., O'connor, E., DeBar, L. L., Kelleher, C., . . . Nunley, S. (2002). Overcoming depression on the Internet (ODIN): a randomized controlled trial of an Internet depression skills intervention program. *Journal of medical internet research*, *4*(3), e14.

Clarke, M. J. (2005). Individual patient data meta-analyses. *Best Practice & Research Clinical Obstetrics & Gynaecology*, *19*(1), 47-55.

Clement, S., Schauman, O., Graham, T., Maggioni, F., Evans-Lacko, S., Bezborodovs, N., . . . Thornicroft, G. (2015). What is the impact of mental health-related stigma on help-seeking? A systematic review of quantitative and qualitative studies. *Psychological medicine*, *45*(1), 11-27.

Cohen, J. (1988). Statistical analysis for the behavioral sciences. *Hillsdale: Lawrance Erlbaum*.

Cooper, H., & Patall, E. A. (2009). The relative benefits of meta-analysis conducted with individual participant data versus aggregated data. *Psychological methods*, *14*(2), 165.

Cooper, P. J., Murray, L., Wilson, A., & Romaniuk, H. (2003). Controlled trial of the short- and long-term effect of psychological treatment of post-partum depression. 1. Impact on maternal mood. *The British Journal of Psychiatry*, *182*(5), 412-419.

Cramer, H., Salisbury, C., Conrad, J., Eldred, J., & Araya, R. (2011). Group cognitive behavioural therapy for women with depression: pilot and feasibility study for a randomised controlled trial using mixed methods. *BMC psychiatry*, *11*(1), 82.

Cristea, I. A., Stefan, S., Karyotaki, E., David, D., Hollon, S. D., & Cuijpers, P. (2017). The effects of cognitive behavioral therapy are not systematically falling: A revision of Johnsen and Friborg (2015): American Psychological Association.

Cuijpers, P. (1998). Minimising interventions in the treatment and prevention of depression. Taking the consequences of the'Dodo Bird Verdict'. *Journal of Mental Health*, *7*(4), 355-365.

Cuijpers, P. (2014). Combined pharmacotherapy and psychotherapy in the treatment of mild to moderate major depression? *JAMA Psychiatry*, *71*(7), 747-748.

Cuijpers, P. (2014). Personalized treatment for functional outcome in depression. *Medicographia*, *36*(4).

Cuijpers, P. (2016). Meta-analyses in mental health research. A practical guide. (V. Universiteit Ed.). Amsterdam.

Cuijpers, P., & Dekker, J. (2005). Psychological treatment of depression; a systematic review of meta-analyses. *Nederlands Tijdschrift voor Geneeskunde*, *149*(34), 1892-1897.

Cuijpers, P., Andersson, G., Donker, T., & van Straten, A. (2011). Psychological treatment of depression: results of a series of meta-analyses. *Nordic journal of psychiatry*, *65*(6), 354-364.

Cuijpers, P., Beekman, A. T., & Reynolds, C. F., 3rd. (2012). Preventing depression: a global priority. *Jama*, *307*(10), 1033-1034.

Cuijpers, P., Berking, M., Andersson, G., Quigley, L., Kleiboer, A., & Dobson, K. S. (2013a). A meta-analysis of cognitive-behavioural therapy for adult depression, alone and in comparison with other treatments. *The Canadian Journal of Psychiatry*, *58*(7), 376-385.

Cuijpers, P., De Wit, L., Weitz, E., Andersson, G., & Huibers, M. J. (2015). The combination of psychotherapy and pharmacotherapy in the treatment of adult depression: a comprehensive meta-analysis. *Journal of Evidence-Based Psychotherapies*, *15*(2), 147.

Cuijpers, P., Dekker, J., Hollon, S. D., & Andersson, G. (2009). Adding psychotherapy to pharmacotherapy in the treatment of depressive disorders in adults: A meta-analysis. *Journal of Clinical Psychiatry*, *70*(9), 1219-1229.

Cuijpers, P., Donker, T., Johansson, R., Mohr, D. C., van Straten, A., & Andersson, G. (2011). Self-guided psychological treatment for depressive symptoms: a meta-analysis. *PLoS One*, *6*(6), e21274.

Cuijpers, P., Donker, T., van Straten, A., Li, J., & Andersson, G. (2010). Is guided self-help as effective as face-to-face psychotherapy for depression and anxiety disorders? A systematic review and meta-analysis of comparative outcome studies. *Psychological Medicine*, *40*(12), 1943-1957.

Cuijpers, P., Donker, T., Weissman, M. M., Ravitz, P., & Cristea, I. A. (2016). Interpersonal psychotherapy for mental health problems: a comprehensive meta-analysis. *American Journal of Psychiatry*, *173*(7), 680-687.

Cuijpers, P., Geraedts, A. S., van Oppen, P., Andersson, G., Markowitz, J. C., & van Straten, A. (2011). Interpersonal psychotherapy for depression: a meta-analysis. *American Journal of Psychiatry*, *168*(6), 581-592.

Cuijpers, P., Hollon, S. D., van Straten, A., Bockting, C., Berking, M., & Andersson, G. (2013). Does cognitive behaviour therapy have an enduring effect that is superior to keeping patients on continuation pharmacotherapy? A meta-analysis. *BMJ Open*, *3*(4), e002542.

Cuijpers, P., Karyotaki, E., Weitz, E., Andersson, G., Hollon, S. D., & van Straten, A. (2014). The effects of psychotherapies for major depression in adults on remission, recovery and improvement: a meta-analysis. *Journal of affecive Disorders*, *159*, 118-126.

Cuijpers, P., Kleiboer, A., Karyotaki, E., & Riper, H. (2017). Internet and mobile interventions for depression: Opportunities and challenges. *Depression and Anxiety*. doi:10.1002/da.22641

Cuijpers, P., Reynolds, C. F., Donker, T., Li, J., Andersson, G., & Beekman, A. (2012). Personalized treatment of adult depression: Medication, psychotherapy, or both? A systematic review. *Depression and Anxiety*, *29*(10), 855-864.

Cuijpers, P., Sijbrandij, M., Koole, S. L., Andersson, G., Beekman, A. T., & Reynolds, C. F., 3rd. (2013). The efficacy of psychotherapy and pharmacotherapy in treating depressive and anxiety disorders: a meta-analysis of direct comparisons. *World Psychiatry*, *12*(2), 137-148.

Cuijpers, P., Sijbrandij, M., Koole, S. L., Andersson, G., Beekman, A. T., & Reynolds, C. F., 3rd. (2014). Adding psychotherapy to antidepressant medication in depression and anxiety disorders: a meta-analysis. *World Psychiatry*, *13*(1), 56-67. doi:10.1002/wps.20089

Cuijpers, P., Smit, F., Bohlmeijer, E., Hollon, S. D., & Andersson, G. (2010). Efficacy of cognitive–behavioural therapy and other psychological treatments for adult depression: meta-analytic study of publication bias. *The British Journal of Psychiatry*, *196*(3), 173-178.

Cuijpers, P., Van Straten, A., & Andersson, G. (2008). Internet-administered cognitive behavior therapy for health problems: a systematic review. *Journal of behavioral medicine*, *31*(2), 169-177.

Cuijpers, P., Van Straten, A., & Warmerdam, L. (2007a). Behavioral activation treatments of depression: A meta-analysis. *Clinical psychology review*, *27*(3), 318-326.

Cuijpers, P., van Straten, A., & Warmerdam, L. (2007b). Problem solving therapies for depression: a meta-analysis. *European psychiatry*, *22*(1), 9-15.

Cuijpers, P., van Straten, A., & Warmerdam, L. (2008). Are individual and group treatments equally effective in the treatment of depression in adults?: A meta-analysis. *The European Journal of Psychiatry*, *22*(1), 38-51.

Cuijpers, P., van Straten, A., Andersson, G., & van Oppen, P. (2008a). Psychotherapy for depression in adults: a meta-analysis of comparative outcome studies. *Journal of consulting and clinical psychology*, *76*(6), 909.

Cuijpers, P., van Straten, A., Bohlmeijer, E., Hollon, S., & Andersson, G. (2010a). The effects of psychotherapy for adult depression are overestimated: a meta-analysis of study quality and effect size. *Psychological medicine*, *40*(2), 211-223.

Cuijpers, P., van Straten, A., Bohlmeijer, E., Hollon, S., & Andersson, G. (2010b). The effects of psychotherapy for adult depression are overestimated: a meta-analysis of study quality and effect size. *Psychological medicine*, *40*(02), 211-223.

Cuijpers, P., van Straten, A., van Oppen, P., & Andersson, G. (2008). Are psychological and pharmacologic interventions equally effective in the treatment of adult depressive disorders? A meta-analysis of comparative studies. *Journal of Clinical Psychiatry*, *69*(11), 1675-1685; quiz 1839-1641.

Cuijpers, P., van Straten, A., Warmerdam, L., & Andersson, G. (2008). Psychological treatment of depression: A meta-analytic database of randomized studies. *BMC Psychiatry*, *8*(1), 1-6.

Cuijpers, P., van Straten, A., Warmerdam, L., & Andersson, G. (2009). Psychotherapy versus the combination of psychotherapy and pharmacotherapy in the treatment of depression: a meta-analysis. *Depression and anxiety*, *26*(3), 279-288.

Davidson, J., Turnbull, C. D., Strickland, R., Miller, R., & Graves, K. (1986). The MontgomeryβÅsberg Depression Scale: reliability and validity. *Acta psychiatrica scandinavica*, *73*(5), 544-548.

De Graaf, L. E., Gerhards, S. A. H., Arntz, A., Riper, H., Metsemakers, J. F. M., Evers, S. M. A. A., ... & Huibers, M. J. H. (2011). One-year follow-up results of unsupported online computerized cognitive behavioural therapy for depression in primary care: A randomized trial. *Journal of behavior therapy and experimental psychiatry*, *42*(1), 89-95.

de Graaf, L. E., Gerhards, S. A., Arntz, A., Riper, H., Metsemakers, J. F., Evers, S. M., . . . Huibers, M. J. (2009). Clinical effectiveness of online computerised cognitive-behavioural therapy without support for depression in primary care: Randomised trial. *The British Journal of Psychiatry*, *195*(1), 73-80. doi:10.1192/bjp.bp.108.054429

de Graaf, L. E., Gerhards, S., Arntz, A., Riper, H., Metsemakers, J., Evers, S., . . . Huibers, M. (2009). Clinical effectiveness of online computerised cognitive–behavioural therapy without support for depression in primary care: randomised trial. *The British Journal of Psychiatry*, *195*(1), 73-80.

de Jonghe, F., Hendricksen, M., van Aalst, G., Kool, S., Peen, V., Van, R., . . . Dekker, J. (2004). Psychotherapy alone and combined with pharmacotherapy in the treatment of depression. *British journal of Psychiatry*, *185*, 37-45.

de Jonghe, F., Kool, S., van Aalst, G., Dekker, J., & Peen, J. (2001). Combining psychotherapy and antidepressants in the treatment of depression. *Journal of affective disorders*, *64*(2-3), 217-229.

de Maat, S. M., Dekker, J., Schoevers, R. A., & de Jonghe, F. (2007). Relative efficacy of psychotherapy and combined therapy in the treatment of depression: a meta-analysis. *European psychiatry*, *22*(1), 1-8.

Debray, T. P., Moons, K. G., Abo-Zaid, G. M. A., Koffijberg, H., & Riley, R. D. (2013). Individual participant data meta-analysis for a binary outcome: one-stage or two-stage? *PLoS One*, *8*(4), e60650.

Deeks, J. J., Higgins, J., & Altman, D. G. (2008). Analysing Data and Undertaking MetaβAnalyses. *Cochrane Handbook for Systematic Reviews of Interventions: Cochrane Book Series*, 243-296.

Dennis, C. L., Ross, L. E., & Grigoriadis, S. (2007). Psychosocial and psychological interventions for treating antenatal depression. *Cochrane Database Syst Rev*(3), CD006309.

DerSimonian, R., & Laird, N. (1986). Meta-analysis in clinical trials. *Controlled clinical trials*, *7*(3), 177-188.

Dimidjian, S., & Hollon, S. D. (2010). How would we know if psychotherapy were harmful? *American psychologist*, *65*(1), 21.

Dobson, D., & Dobson, K. S. (2016). *Evidence-based practice of cognitive-behavioral therapy*. New York: Guilford Publications.

Domino, M. E., Burns, B. J., Silva, S. G., Kratochvil, C. J., Vitiello, B., Reinecke, M. A., . . . March, J. S. (2008). Cost-effectiveness of treatments for adolescent depression: results from TADS. *American journal of Psychiatry*, *165*(5), 588-596

Domino, M., Foster, E., Vitiello, B., Kratochvil, C., Burns, B., Silva, S., . . . March, J. (2009). Relative cost-effectiveness of treatments for adolescent depression: 36-week results from the TADS randomized trial. *Journal of the American Academy of Child & Adolescent Psychiatry*, *48*(7), 711-720.

Donker, T., Batterham, P., Warmerdam, L., Bennett, K., Bennett, A., Cuijpers, P., . . . Christensen, H. (2013). Predictors and moderators of response to internet-delivered Interpersonal Psychotherapy and Cognitive Behavior Therapy for depression. *Journal of affective disorders*, *151*(1), 343-351.

Donker, T., Bennett, K., Bennett, A., Mackinnon, A., van Straten, A., Cuijpers, P., . . . Griffiths, K. M. (2013). Internet-delivered interpersonal psychotherapy versus internet-delivered cognitive behavioral therapy for adults with depressive symptoms: randomized controlled noninferiority trial. *Journal of Medical Internet Research*, *15*(5), e82.

Donker, T., Blankers, M., Hedman, E., Ljotsson, B., Petrie, K., & Christensen, H. (2015). Economic evaluations of Internet interventions for mental health: a systematic review. *Psychological medicine*, *45*(16), 3357-3376.

Donkin, L., Christensen, H., Naismith, S. L., Neal, B., Hickie, I. B., & Glozier, N. (2011). A systematic review of the impact of adherence on the effectiveness of e-therapies. *Journal of medical Internet research*, *13*(3), e52.

Donohue, J. M., & Pincus, H. A. (2007). Reducing the societal burden of depression. *Pharmacoeconomics*, *25*(1), 7-24.

Dowrick, C., Dunn, G., Ayuso-Mateos, J. L., Dalgard, O. S., Page, H., & Lehtinen, V. (2000). Problem solving treatment and group psychoeducation for depression: multicentre randomised controlled trial. *BMJ*, (7274), 1450-1454.

Driessen, E., Cuijpers, P., de Maat, S. C., Abbass, A. A., de Jonghe, F., & Dekker, J. J. (2010). The efficacy of short-term psychodynamic psychotherapy for depression: a meta-analysis. *Clinical psychology review*, *30*(1), 25-36.

Driessen, E., Cuijpers, P., Hollon, S. D., & Dekker, J. J. (2010). Does pretreatment severity moderate the efficacy of psychological treatment of adult outpatient depression? A meta-analysis. *Journal of consulting and clinical psychology, 78*(5), 668.

Driessen, E., Hollon, S. D., Bockting, C. L., Cuijpers, P., & Turner, E. H. (2015). Does publication bias inflate the apparent efficacy of psychological treatment for major depressive disorder? A systematic review and meta-analysis of US National Institutes of Health-funded trials. *PLoS One*, *10*(9), e0137864.

Duarte, P. S., Miyazaki, M. C., Blay, S. L., & Sesso, R. (2009). Cognitive–behavioral group therapy is an effective treatment for major depression in hemodialysis patients. *Kidney international*, *76*(4), 414-421.

Duval, S., & Tweedie, R. (2000). Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*, *56*(2), 455-463.

Dwight-Johnson, M., Aisenberg, E., Golinelli, D., Hong, S., O'Brien, M., & Ludman, E. (2011). Telephone-based cognitive-behavioral therapy for Latino patients living in rural areas: a randomized pilot study. *Psychiatric Services*, *62*(8), 936-942.

D'Zurilla, T. J., & Nezu, A. M. (1999). Problem-solving therapy: A social competence approach to clinical intervention. New York: Springer Publishing Company.

Ebert, D. D., Berking, M., Cuijpers, P., Lehr, D., Pörtner, M., & Baumeister, H. (2015). Increasing the acceptance of internet-based mental health interventions in primary care patients with depressive symptoms. A randomized controlled trial. *Journal of affective disorders*, *176*, 9-17.

Ebert, D. D., Donkin, L., Andersson, G., Andrews, G., Berger, T., Carlbring, P., . . . Cuijpers, P. (2016). Does Internet-based guided-self-help for depression cause harm? An individual participant data meta-analysis on deterioration rates and its moderators in randomized controlled trials. *Psychological Medicine*, *46*(13), 2679-2693.

Ebert, D. D., Lehr, D., Baumeister, H., Boß, L., Riper, H., Cuijpers, P., . . . Berking, M. (2014). GET. ON Mood Enhancer: efficacy of Internet-based guided self-help compared to psychoeducation for depression: an investigator-blinded randomised controlled trial. *Trials, 15*(1), 39.

Ebert, D. D., Lehr, D., Boß, L., Riper, H., Cuijpers, P., Andersson, G., . . . Berking, M. (2014). Efficacy of an internet-based problem-solving training for teachers: results of a randomized controlled trial. *Scandinavian journal of work, environment & health*, *40*(6), 582-596.

Egger, M., Davey Smith, G., Schneider, M., & Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ*, *315*(7109), 629-634.

Ekers, D., Godfrey, C., Gilbody, S., Parrott, S., Richards, D. A., Hammond, D., & Hayes, A. (2011). Cost utility of behavioural activation delivered by the non-specialist. *Br J Psychiatry, 199*(6), 510-511.

Ekers, D., Webster, L., Van Straten, A., Cuijpers, P., Richards, D., & Gilbody, S. (2014). Behavioural activation for depression; an update of meta-analysis of effectiveness and sub group analysis. *PloS one*, *9*(6), e100100.

Elkin, I., Shea, M. T., Watkins, J. T., Imber, S. D., Sotsky, S. M., Collins, J. F., ... & Fiester, S. J. (1989). National Institute of Mental Health treatment of depression collaborative research program: General effectiveness of treatments. *Archives of general psychiatry*, *46*(11), 971-982.

Etchegoyen, R. H. (2005). The fundamentals of psychoanalytic technique. London: Karnac Books.

Evangelou, E., Ioannidis, J. P., & Patsopoulos, N. A. (2007). Uncertainty in heterogeneity estimates in meta-analyses. *BMJ: British Medical Journal*, *335*(7626), 914-916.

Evans, M. D., Hollon, S. D., DeRubeis, R. J., Piasecki, J. M., Grove, W. M., Garvey, M. J., & Tuason, V. B. (1992). Differential relapse following cognitive therapy and pharmacotherapy for depression. *Archives of general psychiatry*, *49*(10), 802-808.

Evans, R. L., & Connis, R. T. (1995). Comparison of brief group therapies for depressed cancer patients receiving radiation treatment. *Public health reports*, *110*(3), 306.

Fantino, B., & Moore, N. (2009). The self-reported Montgomery-Åsberg depression rating scale is a useful evaluative tool in major depressive disorder. *BMC Psychiatry*, *9*(1), 26.

Faramarzi, M., Alipor, A., Esmaelzadeh, S., Kheirkhah, F., Poladi, K., & Pash, H. (2008). Treatment of depression and anxiety in infertile women: Cognitive behavioral therapy versus fluoxetine. *Journal of affective disorders*, *108*(1-2), 159-164.

Farrer, L., Christensen, H., Griffiths, K. M., & Mackinnon, A. (2011). Internet-based CBT for depression with and without telephone tracking in a national helpline: randomised controlled trial. *PLoS One*, *6*(11), e28099.

Fava, G. A., Fabbri, S., & Sonino, N. (2002). Residual symptoms in depression: an emerging therapeutic target. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *26*(6), 1019-1027.

Fischer, A., Schröder, J., Vettorazzi, E., Wolf, O. T., Pöttgen, J., Lau, S., . . . Gold, S. M. (2015). An online programme to reduce depression in patients with multiple sclerosis: a randomised controlled trial. *The Lancet Psychiatry*, *2*(3), 217-223.

Foa, E. B., Hembree, E. A., Cahill, S. P., Rauch, S. A., Riggs, D. S., Feeny, N. C., & Yadin, E. (2005). Randomized trial of prolonged exposure for posttraumatic stress disorder with and without cognitive restructuring: outcome at academic and community clinics. *Journal of consulting and clinical psychology*, *73*(5), 953.

Frank, E., Kupfer, D. J., Perel, J. M., Cornes, C., Jarrett, D. B., Mallinger, A. G., . . . Grochocinski, V. J. (1990). Three-year outcomes for maintenance therapies in recurrent depression. *Archives of General Psychiatry*, *47*(12), 1093-1099.

Frank, E., Prien, R. F., Jarrett, R. B., Keller, M. B., Kupfer, D. J., Lavori, P. W., . . . Weissman, M. M. (1991). Conceptualization and rationale for consensus definitions of terms in major depressive disorder: remission, recovery, relapse, and recurrence. *Archives of General Psychiatry*, *48*(9), 851-855.

Freedland, K. E., Skala, J. A., Carney, R. M., Rubin, E. H., Lustman, P. J., Davila-Roman, V. G., . . . Hogue, C. W., Jr. (2009). Treatment of depression after coronary artery bypass surgery: a randomized controlled trial. *Archives of General Psychiatry*, *66*(4), 387-396.

Furukawa, T. A. (1999). From effect size into number needed to treat. *The Lancet*, *353*(9165), 1680.

Furukawa, T. A., Horikoshi, M., Kawakami, N., Kadota, M., Sasaki, M., Sekiya, Y., . . . Grothaus, L. C. (2012). Telephone cognitive-behavioral therapy for subthreshold depression and presenteeism in workplace: A randomized controlled trial. *PLoS ONE*, *7*(4)

García-Peña, C., Vázquez-Estupiñan, F., Avalos-Pérez, F., Jiménez, L. V. R., Sánchez-Garcia, S., & Juárez-Cedillo, T. (2015). Clinical effectiveness of group cognitive-behavioural therapy for depressed older people in primary care: A randomised controlled trial. *Salud Mental*, *38*(1), 33-39.

Gartlehner, G., Hansen, R. A., Morgan, L. C., Thaler, K., Lux, L., Van Noord, M., . . . Wilkins, T. (2011). Comparative Benefits and Harms of Second-Generation Antidepressants for Treating Major Depressive DisorderAn Updated Meta-analysis. *Annals of Internal Medicine*, *155*(11), 772-785.

Gary, R. A., Dunbar, S. B., Higgins, M. K., Musselman, D. L., & Smith, A. L. (2010). Combined exercise and cognitive behavioral therapy improves outcomes in patients with heart failure. *Journal of psychosomatic research*, *69*(2), 119-131.

Geddes, J. R., Carney, S. M., Davies, C., Furukawa, T. A., Kupfer, D. J., Frank, E., & Goodwin, G. M. (2003). Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. *The Lancet*, *361*(9358), 653-661.

Gelenberg, A. J., Freeman, M. P., Markowitz, J. C., Rosenbaum, J. F., Thase, M. E., Trivedi, M. H., . . . Fawcett, J. A. (2010). Practice guideline for the treatment of patients with major depressive disorder third edition. *The American Journal of Psychiatry*, *167*(10), 1.

Gellatly, J., Bower, P., Hennessy, S., Richards, D., Gilbody, S., & Lovell, K. (2007). What makes self-help interventions effective in the management of depressive symptoms? Meta-analysis and meta-regression. *Psychological Medicine*, *37*(9), 1217-1228.

Geraedts, A. S., Kleiboer, A. M., Wiezer, N. M., van Mechelen, W., & Cuijpers, P. (2014). Short-term effects of a web-based guided self-help intervention for employees with depressive symptoms: Randomized controlled trial. *Journal of medical Internet research*, *16*(5), e121.

Gilbody, S., Littlewood, E., Hewitt, C., Brierley, G., Tharmanathan, P., Araya, R., . . . White, D. (2015). Computerised cognitive behaviour therapy (cCBT) as treatment for depression in primary care (REEACT trial): large scale pragmatic randomised controlled trial. *Bmj*, *351*, h5627.

Gotlib, I. H., & Hammen, C. L. (2008). *Handbook of depression*. New York: Guilford Press.

Greenberg, P. E., & Birnbaum, H. G. (2005). The economic burden of depression in the US: societal and patient perspectives. *Expert opinion on pharmacotherapy*, *6*(3), 369-376.

Grochtdreis, T., Brettschneider, C., Wegener, A., Watzke, B., Riedel-Heller, S., Harter, M., & Konig, H. H. (2015). Cost-effectiveness of collaborative care for the treatment of depressive disorders in primary care: a systematic review. *PLoS One*, *10*(5), e0123078.

Gustavsson, A., Svensson, M., Jacobi, F., Allgulander, C., Alonso, J., Beghi, E., . . . Olesen, J. (2011). Cost of disorders of the brain in Europe 2010. *Eur Neuropsychopharmacol*, *21*(10), 718-779.

Hallgren, M., Kraepelien, M., Öjehagen, A., Lindefors, N., Zeebari, Z., Kaldo, V., & Forsell, Y. (2015). Physical exercise and internet-based cognitive-behavioural therapy in the treatment of depression: Randomised controlled trial. *British Journal of Psychiatry*, *207*(3), 227-234.

Hamamci, Z. (2006). Integrating psychodrama and cognitive behavioral therapy to treat moderate depression. *Arts in Psychotherapy*, (3), 199-207.

Hamdan-Mansour, A. M., Puskar, K., & Bandak, A. G. (2009). Effectiveness of cognitive-behavioral therapy on depressive symptomatology, stress and coping strategies among Jordanian university students. *Issues Ment Health Nurs*, *30*(3), 188-196.

Hamilton, K. E., & Dobson, K. S. (2002). Cognitive therapy of depression: pretreatment patient predictors of outcome. *Clinical psychology review*, *22*(6), 875-893.

Hamilton, M. (1960). A rating scale for depression. *Journal of neurology, neurosurgery, and psychiatry*, *23*(1), 56.

Hanson, K., Webb, T. L., Sheeran, P., & Turpin, G. (2016). Attitudes and preferences towards self-help treatments for depression in comparison to psychotherapy and antidepressant medication. *Behavioural and Cognitive Psychotherapy*, *44*(2), 129-139.

Hedges L, O. I. (2001). *Statistical Models for Meta-Analysis*. New York: Academic Press. Hedges, LV, & Pigott, TD.

Hedges, L., & Olkin, I. (1985). Statistical models for meta-analysis. New York: Academic Press. Hedges, LV, & Pigott, TD (2001). The power of statistical tests in meta-analysis. Psychological Methods, 6, 203-217.

Hedman, E., Ljótsson, B., & Lindefors, N. (2012). Cognitive behavior therapy via the Internet: a systematic review of applications, clinical efficacy and cost–effectiveness. *Expert review of pharmacoeconomics & outcomes research*, *12*(6), 745-764.

Hersen, M., Himmelhoch, J. M., Thase, M. E., & Bellack, A. S. (1984). Effects of social skill training, amitriptyline, and psychotherapy in unipolar depressed women. *Behavior Therapy*, *15*(1), 21-40.

Higgins, J. P., & Green, S. (2008). *Cochrane handbook for systematic reviews of interventions* (Vol. 5): Wiley Online Library.

Higgins, J. P., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *BMJ: British Medical Journal*, *327*(7414), 557.

Higgins, J. P., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *BMJ*, *327*(7414), 557-560.

Higgins, J., & Altman, D. G. (2008). Assessing risk of bias in included studies. *Cochrane Handbook for Systematic Reviews of Interventions: Cochrane Book Series*, 187-241.

Higgins, J., & Green, S. (2011). Handbook for systematic reviews of interventions version 5.1. 0 [updated March 2011]. *The Cochrane Collaboration*.

Higgins, J., Altman, D., Gøtzsche, P., Jüni, P., Moher, D., Oxman, A., . . . Sterne, J. (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj*, *343*, d5928.

Hirschfeld, R. M., Dunner, D. L., Keitner, G., Klein, D. N., Koran, L. M., Kornstein, S. G., . . . Ninan, P. T. (2002). Does psychosocial functioning improve independent of depressive symptoms? A comparison of nefazodone, psychotherapy, and their combination. *Biological psychiatry*, *51*(2), 123-133.

Hollinghurst, S., Carroll, F. E., Abel, A., Campbell, J., Garland, A., Jerrom, B., . . . Wiles, N. (2014). Cost-effectiveness of cognitive-behavioural therapy as an adjunct to pharmacotherapy for treatment-resistant depression in primary care: Economic evaluation of the CoBalT Trial. *British Journal of Psychiatry*, *204*(1), 69-76.

Hollon, S. D., DeRubeis, R. J., Evans, M. D., Wiemer, M. J., Garvey, M. J., Grove, W. M., & Tuason, V. B. (1992). Cognitive therapy and pharmacotherapy for depression. Singly and in combination. *Archives of General Psychiatry*, *49*(10), 774-781.

Hollon, S. D., DeRubeis, R. J., Fawcett, J., Amsterdam, J. D., Shelton, R. C., Zajecka, J., . . . Gallop, R. (2014). Effect of cognitive therapy with antidepressant medications vs antidepressants alone on the rate of recovery in major depressive disorder: a randomized clinical trial. *JAMA Psychiatry*, *71*(10), 1157-1164.

Honey, K. L., Bennett, P., & Morgan, M. (2002). A brief psycho-educational group intervention for postnatal depression. *British Journal of Clinical Psychology*, *41*(4), 405-409.

Hou, Y., Hu, P., Zhang, Y., Lu, Q., Wang, D., Yin, L., . . . Zou, X. (2014). Cognitive behavioral therapy in combination with systemic family therapy improves mild to moderate postpartum depression. *Revista Brasileira de Psiquiatria*, *36*(1), 47-52. doi:10.1590/1516-4446-2013-1170

Hu, T. W. (2006). Perspectives: an international review of the national cost estimates of mental illness, 1990-2003. *The journal of mental health policy and economics*, *9*(1), 3-13.

Huang, C. Y., Lai, H. L., Chen, C. I., Lu, Y. C., Li, S. C., Wang, L. W., & Su, Y. (2015). Effects of motivational enhancement therapy plus cognitive behaviour therapy on depressive symptoms and health-related quality of life in adults with type II diabetes mellitus: A randomised controlled trial. *Quality of Life Research*, *25*(5), 1275-1283.

Imamura, K., Kawakami, N., Furukawa, T. A., Matsuyama, Y., Shimazu, A., Umanodan, R., . . . Kasai, K. (2014). Effects of an Internet-based cognitive behavioral therapy (iCBT) program in Manga format on improving subthreshold depressive symptoms among healthy workers: A randomized controlled trial. *PLoS ONE*, *9*(5), e97167.

Institute for Health Metrics and Evaluation (IHME). (2015). GBD Compare. Retrieved from http://vizhub.healthdata.org/gbd-compare

Ioannidis, J. P., & Trikalinos, T. A. (2007). An exploratory test for an excess of significant findings. *Clinical trials*, *4*(3), 245-253.

Ioannidis, J. P., Patsopoulos, N. A., & Evangelou, E. (2007). Uncertainty in heterogeneity estimates in meta-analyses. *BMJ: British Medical Journal*, *335*(7626), 914.

Ioannidis, J. P., Patsopoulos, N. A., & Evangelou, E. (2007). Uncertainty in heterogeneity estimates in meta-analyses. *BMJ*, *335*(7626), 914-916.

Jacob, K., Sharan, P., Mirza, I., Garrido-Cumbrera, M., Seedat, S., Mari, J. J., . . . Saxena, S. (2007). Mental health systems in countries: where are we now? *The Lancet*, *370*(9592), 1061-1077.

Jacobson, N. S., & Truax, P. (1991). Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. *Journal of consulting and clinical psychology*, *59*(1), 12.

Jacobson, N. S., Dobson, K. S., Truax, P. A., Addis, M. E., Koerner, K., Gollan, J. K., . . . Prince, S. E. (1996). A component analysis of cognitive-behavioral treatment for depression. *Journal of Consulting and Clinical Psychoogyl*, *64*(2), 295-304.

Jansen, J. P., & Naci, H. (2013). Is network meta-analysis as valid as standard pairwise meta-analysis? It all depends on the distribution of effect modifiers. *BMC medicine*, *11*(1), 159.

Jiang, L., Wang, Z. Z., Qiu, L. R., Wan, G. B., Lin, Y., & Wei, Z. (2014). Psychological intervention for postpartum depression. *Journal of Huazhong University of Science and Technology: Medical sciences*, *34*(3), 437-442.

Johansson, R., & Andersson, G. (2012). Internet-based psychological treatments for depression. *Expert review of neurotherapeutics*.

Johansson, R., Ekbladh, S., Hebert, A., Lindstrˆm, M., Mˆller, S., Petitt, E., . . . Andersson, G. (2012). Psychodynamic guided self-help for adult depression through the internet: a randomised controlled trial. *PLoS One*, *7*(5), e38021..

Johansson, R., Sjöberg, E., Sjögren, M., Johnsson, E., Carlbring, P., Andersson, T., . . . Andersson, G. (2012). Tailored vs. standardized internet-based cognitive behavior therapy for depression and comorbid symptoms: a randomized controlled trial. *PLoS One*, *7*(5), e36905.

Jones, A. P., Riley, R. D., Williamson, P. R., & Whitehead, A. (2009). Meta-analysis of individual patient data versus aggregate data from longitudinal clinical trials. *Clinical trials*, *6*(1), 16-27.

Jonsson, U., Alaie, I., Parling, T., & Arnberg, F. K. Reporting of harms in randomized controlled trials of psychological interventions for mental and behavioral disorders: A review of current practice. *Contemporary Clinical Trials*, *38*(1), 1-8.

Jorm, A. F. (2009). Evaluations of Web-based psychological interventions need to avoid the re-test artefact. *Australian and New Zealand journal of psychiatry*, *43*(9), 877-877.

Kaltenthaler, E., Brazier, J., De Nigris, E., Tumur, I., Ferriter, M., Beverley, C., . . . Sutcliffe, P. (2006). Computerised cognitive behaviour therapy for depression and anxiety update: a systematic review and economic evaluation. *Health Technology Assessment*, *10*(33), iii, xi-xiv, 1-168.

Karp, J. F., Buysse, D. J., Houck, P. R., Cherry, C., Kupfer, D. J., & Frank, E. (2004). Relationship of variability in residual symptoms with recurrence of major depressive disorder during maintenance treatment. *American Journal of Psychiatry*, *161*(10), 1877-1884.

Karyotaki, E., Kleiboer, A., Smit, F., Turner, D. T., Pastor, A. M., Andersson, G., . . . Cuijpers, P. (2015). Predictors of treatment dropout in self-guided web-based interventions for depression: an 'individual patient data' meta-analysis. *Psychoogical Medicine*, *45*(13), 2717-2726.

Karyotaki, E., Riper, H., Twisk, J., Hoogendoorn, A., Kleiboer, A., Mira, A., . . . Littlewood, E. (2017). Efficacy of self-guided internet-based cognitive behavioral therapy in the treatment of depressive symptoms: a meta-analysis of individual participant data. *JAMA Psychiatry*, *74*(4), 351-359.

Karyotaki, E., Smit, Y., Beurs, D. P., Henningsen, K. H., Robays, J., Huibers, M. J., ... & Cuijpers, P. (2016). The longβterm efficacy of acuteβphase psychotherapy for depression: a metaβanalysis of randomized trials. *Depression and anxiety*, *33*(5), 370-383.

Karyotaki, E., Smit, Y., Henningsen, K. H., Huibers, M. J. H., Robays, J., de Beurs, D., & Cuijpers, P. (2016). Combining pharmacotherapy and psychotherapy or monotherapy for major depression? A meta-analysis on the long-term effects. *Journal of affective disorders*, *194*, 144-152.

Kay-Lambkin, F. J., Baker, A. L., Lewin, T. J., & Carr, V. J. (2009). Computer-based psychological treatment for comorbid depression and problematic alcohol and/or cannabis use: A randomized controlled trial of clinical efficacy. *Addiction*, *104*(3), 378-388.

Keller, M. B. (1994). Depression: a long-term illness. *The British Journal of Psychiatry*.

Keller, M. B. (2003). Past, present, and future directions for defining optimal treatment outcome in depression: remission and beyond. *Jama*, *289*(23), 3152-3160.

Kennard, B. D., Silva, S. G., Tonev, S., Rohde, P., Hughes, J. L., Vitiello, B., . . . Reinecke, M. (2009). Remission and recovery in the Treatment for Adolescents with Depression Study (TADS): acute and long-term outcomes. *Journal of the American Academy of Child & Adolescent Psychiatry*, *48*(2), 186-195.

Kennedy, S. H. (2013). A review of antidepressant therapy in primary care: Current practices and future directions. *Primary Care Companion to the Journal of Clinical Psychiatry*, *15*(2).

Kenter, R. M. F., Cuijpers, P., Beekman, A., & van Straten, A. (2016). Effectiveness of a Web-based guided self-help intervention for outpatients with a depressive disorder: Short-term results from a randomized controlled trial. *Journal of medical Internet research*, *18*(3).

Kessler, D., Lewis, G., Kaur, S., Wiles, N., King, M., Weich, S., . . . Peters, T. J. (2009). Therapist-delivered Internet psychotherapy for depression in primary care: a randomised controlled trial. *The Lancet*, *9690*, 628-634.

Kessler, R. C., Berglund, P. A., Bruce, M. L., Koch, J. R., Laska, E. M., Leaf, P. J., . . . Wang, P. S. (2001). The prevalence and correlates of untreated serious mental illness. *Health services research*, *36*(6 Pt 1), 987.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*, *62*(6), 593-602.

Kessler, R. C., Chiu, W. T., Demler, O., & Walters, E. E. (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*, *62*(6), 617-627.

Khan, A., Faucett, J., Lichtenberg, P., Kirsch, I., & Brown, W. A. (2012). A systematic review of comparative efficacy of treatments and controls for depression. *PLoS One*, *7*(7), e41778.

Kiluk, B. D., Sugarman, D. E., Nich, C., Gibbons, C. J., Martino, S., Rounsaville, B. J., & Carroll, K. M. (2011). A methodological analysis of randomized clinical trials of computer-assisted therapies for psychiatric disorders: toward improved standards for an emerging field. *American Journal of Psychiatry*, *168*(8), 790-799.

King, M., Sibbald, B., Ward, E., Bower, P., Lloyd, M., Gabbay, M., & Byford, S. (2000). Randomised controlled trial of non-directive counselling, cognitive-behaviour therapy and usual general practitioner care in the management of depression as well as mixed anxiety and depression in primary care. *Health Technol Assess*, *4*(19), 1-83.

Kirsch, I., & Low, C. B. (2013). Suggestion in the treatment of depression. *American Journal of Clinical Hypnosis*, *55*(3), 221-229.

Kirsch, I., Deacon, B. J., Huedo-Medina, T. B., Scoboria, A., Moore, T. J., & Johnson, B. T. (2008). Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. *PLoS Med*, *5*(2), e45.

Kivi, M., Eriksson, M. C. M., Hange, D., Petersson, E.-L., Vernmark, K., Johansson, B., & Björkelund, C. (2014). Internet-based therapy for mild to moderate depression in Swedish primary care: Short term results from the PRIM-NET randomized controlled trial. *Cognitive Behaviour Therapy*, *43*(4), 289-298.

Kleiboer, A., Donker, T., Seekles, W., van Straten, A., Riper, H., & Cuijpers, P. (2015). A randomized controlled trial on the role of support in internet-based problem solving therapy for depression and anxiety. *Behav Res Ther*, *72*, 63-71.

Klein, J. P., Berger, T., Schröder, J., Späth, C., Meyer, B., Caspar, F., . . . Gräfe, V. (2016). Effects of a Psychological Internet Intervention in the Treatment of Mild to Moderate Depressive Symptoms: Results of the EVIDENT Study, a Randomized Controlled Trial. *Psychotherapy and psychosomatics*, *85*(4), 218-228.

Klein, J. P., Berger, T., Schröder, J., Späth, C., Meyer, B., Caspar, F., ... & Hautzinger, M. (2016). Effects of a psychological internet intervention in the treatment of mild to moderate depressive symptoms: results of the EVIDENT study, a randomized controlled trial. *Psychotherapy and psychosomatics*, *85*(4), 218-228.

Knapp, M., Romeo, R., Mogg, A., Eranti, S., Pluck, G., Purvis, R., . . . McLoughlin, D. M. (2008). Cost-effectiveness of transcranial magnetic stimulation vs. electroconvulsive therapy for severe depression: a multi-centre randomised controlled trial. *Journal of affective disorders*, *109*(3), 273-285.

Kohn, R., Saxena, S., Levav, I., & Saraceno, B. (2004). The treatment gap in mental health care. *Bulletin of the World health Organization*, *82*(11), 858-866.

Kolovos, S., Kleiboer, A., & Cuijpers, P. (2016). Effect of psychotherapy for depression on quality of life: meta-analysis. *The British Journal of Psychiatry*, bjp. bp. 115.175059.

Kolovos, S., van Tulder, M. W., Cuijpers, P., Prigent, A., Chevreul, K., Riper, H., & Bosmans, J. E. (2017). The effect of treatment as usual on major depressive disorder: A meta-analysis. *Journal of affective disorders*, *210*, 72-81.

Koppers, D., Peen, J., Niekerken, S., Van, R., & Dekker, J. (2011). Prevalence and risk factors for recurrence of depression five years after short term psychodynamic therapy. *Journal of affective disorders*, *134*(1-3), 468-472.

Koran, L. M., Hanna, G. L., Hollander, E., Nestadt, G., & Simpson, H. B. (2007). Practice guideline for the treatment of patients with obsessive-compulsive disorder. *The American Journal of Psychiatry*, *164*(7), 1.

Kroenke, K., Spitzer, R. L., & Williams, J. B. (2001). The PHQ-9: validity of a brief depression severity measure. *Journal of General Internal Medicine*, *16*(9), 606-613.

Kruijshaar, M. E., Barendregt, J., Vos, T., de Graaf, R., Spijker, J., & Andrews, G. (2005). Lifetime prevalence estimates of major depression: an indirect estimation method and a quantification of recall bias. *European journal of epidemiology*, *20*(1), 103-111.

Kwan, B. M., Dimidjian, S., & Rizvi, S. L. (2010). Treatment preference, engagement, and clinical improvement in pharmacotherapy versus psychotherapy for depression. *Behaviour research and therapy*, *48*(8), 799-804.

Laidlaw, K., Davidson, K., Toner, H., Jackson, G., Clark, S., Law, J., ... & Cross, S. (2008). A randomised controlled trial of cognitive behaviour therapy vs treatment as usual in the treatment of mild to moderate late life depression. *International journal of geriatric psychiatry*, *23*(8), 843-850.

Lam, R. W., Kennedy, S. H., Grigoriadis, S., McIntyre, R. S., Milev, R., Ramasubbu, R., . . . Ravindran, A. V. (2009). Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical guidelines for the management of major depressive disorder in adults.: III. Pharmacotherapy. *Journal of affective disorders*, *117*, S26-S43.

Lambert, M. J., Bergin, A., Bergin, A., & Garfield, S. (1993). *Handbook of psychotherapy and behavior change*. New York: John Wiley & Sons.

Lamers, F., Jonkers, C. C., Bosma, H., Kempen, G. I., Meijer, J. A., Penninx, B. W., . . . Eijk, J. T. (2010). A minimal psychological intervention in chronically ill elderly patients with depression: a randomized trial. *Psychotherapy and Psychosomatics*, *79*(4), 217-226.

Laupacis, A., Sackett, D. L., & Roberts, R. S. (1988). An assessment of clinically useful measures of the consequences of treatment. *New England Journal of Medicine*, *318*(26), 1728-1733.

Lepine, J. P., & Briley, M. (2011). The increasing burden of depression. *Neuropsychiatric disease and Treatment*, *7*(Suppl 1), 3-7.

Leung, S. S., Lee, A. M., Chiang, V. C., Lam, S. K., Kuen, Y. W., & Wong, D. F. (2013). Culturally sensitive, preventive antenatal group cognitive-behavioural therapy for Chinese women with depression. *Internationan Journal of Nursing Practice*, *19*(Supp 1), 28-37.

Lewinsohn, P. M. (1974). A behavioral approach to depression. *Essential papers on depression*, 150-172.

Link, B. G., & Phelan, J. C. (2001). Conceptualizing stigma. *Annual review of Sociology*, *27*(1), 363-385.

Liu, E. T.-H., Chen, W.-L., Li, Y.-H., Wang, C. H., Mok, T. J., & Huang, H. S. (2009). Exploring the efficacy of cognitive bibliotherapy and a potential mechanism of change in the treatment of depressive symptoms among the Chinese: A randomized controlled trial. *Cognitive Therapy and Research*, *33*(5), 449-461.

Luborsky, L. (1995). Are Common Factors Across Different Psychotherapies the Main Explanation for the Dodo Bird Verdict That "Everyone Has Won So All Shall Have Prizes"? *Clinical Psychology: Science and Practice*, *2*(1), 106-109.

Lustman, P. J., Griffith, L. S., Freedland, K. E., Kissel, S. S., & Clouse, R. E. (1998). Cognitive behavior therapy for depression in type 2 diabetes mellitus. A randomized, controlled trial. *Annals of Internal Medicine*, *8*, 613-621.

Lynch, F. L., Dickerson, J. F., Garber, J., Clarke, G. N., Weersing, V. R., Beardslee, W. R., . . . DeBar, L. L. (2011). Cost-effectiveness of a cognitive behavioral intervention to prevent depression in at-risk teens. *Journal of Mental Health Policy and Economics*, *14*, S19.

Macaskill, N. D., & Macaskill, A. (1996). Rational-emotive therapy plus pharmacotherapy versus pharmacotherapy alone in the treatment of high cognitive dysfunction depression. *Cognitive Therapy Research*, *20*(6), 575-592.

Mack, S., Jacobi, F., Gerschler, A., Strehle, J., Höfler, M., Busch, M. A., . . . Gaebel, W. (2014). Selfβreported utilization of mental health services in the adult German population–evidence for unmet needs? Results of the DEGS1βMental Health Module (DEGS1βMH). *International journal of methods in psychiatric research*, *23*(3), 289-303.

MacPherson, H., Richmond, S., Bland, M., Brealey, S., Gabe, R., Hopton, A., . . . Watt, I. (2013). Acupuncture and counselling for depression in primary care: A randomised controlled trial. *PLoS Med*, *10*(9), e1001518.

Maina, G., Rosso, G., & Bogetto, F. (2009). Brief dynamic therapy combined with pharmacotherapy in the treatment of major depressive disorder: long-term results. *Journal of affective disorders*, *114*(1), 200-207.

Maina, G., Rosso, G., Rigardetto, S., Piat, S. C., & Bogetto, F. (2010). No effect of adding brief dynamic therapy to pharmacotherapy in the treatment of obsessive-compulsive disorder with concurrent major depression. *Psychotherapy and Psychosomatics*, *79*(5), 295-302.

Maljanen, T., Paltta, P., Harkanen, T., Virtala, E., Lindfors, O., Laaksonen, M. A., & Knekt, P. (2012). The cost-effectiveness of short-term psychodynamic psychotherapy and solution-focused therapy in the treatment of depressive and anxiety disorders during a one-year follow-up. *The journal of mental health policy and economics*, *15*(1), 13-23.

Markowitz, J. C. (2008). Evidence-based psychotherapies for depression. *Journal of Occupational and Environmental Medicine*, *50*(4), 437-440.

Markowitz, J. C., Svartberg, M., & Swartz, H. A. (1998). Is IPT time-limited psychodynamic psychotherapy?. *The Journal of psychotherapy practice and research*, *7*(3), 185.

Marks, I., & Cavanagh, K. (2009). Computer-aided psychological treatments: evolving issues. *Annual Review of Clinical Psychology*, *5*, 121-141.

McHugh, R. K., Whitton, S. W., Peckham, A. D., Welge, J. A., & Otto, M. W. (2013). Patient preference for psychological vs. pharmacological treatment of psychiatric disorders: a meta-analytic review. *The Journal of clinical psychiatry*, *74*(6), 595-602.

Meyer, B., Berger, T., Caspar, F., Beevers, C. G., Andersson, G., & Weiss, M. (2009). Effectiveness of a novel integrative online treatment for depression (Deprexis): randomized controlled trial. *Journal of Medical Internet Research*, *11*(2), e15.

Meyer, B., Bierbrodt, J., Schröder, J., Berger, T., Beevers, C. G., Weiss, M., . . . Klein, J. P. (2015). Effects of an Internet intervention (Deprexis) on severe depression symptoms: Randomized controlled trial. *Internet Interventions*, *2*(1), 48-59.

Miller, I. W., Norman, W. H., & Keitner, G. I. (1989). Cognitive-behavioral treatment of depressed inpatients: six- and twelve-month follow-up. *American Journal of Psychiatry*, *146*(10), 1274-1279.

Miller, W., Anton, H., & Townson, A. (2008). Measurement properties of the CESD scale among individuals with spinal cord injury. *Spinal cord*, *46*(4), 287-292.

Mira, A., Bretón-López, J., García-Palacios, A., Quero, S., Baños, R. M., & Botella, C. (In press). An Internet-based program for depressive symptoms using human and automated support: A randomized control trial. *Neuropsychiatric Disease and Treatment*.

Miranda, J., Chung, J. Y., Green, B. L., Krupnick, J., Siddique, J., Revicki, D. A., & Belin, T. (2003). Treating Depression in Predominantly Low-Income Young Minority Women: A Randomized Controlled Trial. *JAMA: Journal of the American Medical Association*, *290*(1), 57-65.

Miranda, J., Green, B. L., Krupnick, J. L., Chung, J., Siddique, J., Belin, T., & Revicki, D. (2006). One-year outcomes of a randomized clinical trial treating depression in low-income minority women. *Journal of consulting and clinical psychology*, *74*(1), 99.

Mohr, D. C., Beutler, L. E., Engle, D., Shoham-Salomon, V., Bergan, J., Kaszniak, A. W., & Yost, E. B. (1990). Identification of patients at risk for nonresponse and negative outcome in psychotherapy. *Journal of consulting and clinical psychology*, *58*(5), 622.

Mohr, D. C., Carmody, T., Erickson, L., Jin, L., & Leader, J. (2011). Telephone-administered cognitive behavioral therapy for veterans served by community-based outpatient clinics *Journal of consulting and clinical psychology*, *79*(2), 261-265.

Mohr, D. C., Cuijpers, P., & Lehman, K. (2011). Supportive accountability: a model for providing human support to enhance adherence to eHealth interventions. *Journal of Medical Internet Research*, *13*(1), e30.

Mohr, D. C., Hart, S. L., Howard, I., Julian, L., Vella, L., Catledge, C., & Feldman, M. D. (2006). Barriers to psychotherapy among depressed and nondepressed primary care patients. *Annals of Behavioral Medicine*, *32*(3), 254-258.

Mohr, D. C., Ho, J., Duffecy, J., Baron, K. G., Lehman, K. A., Jin, L., & Reifler, D. (2010). Perceived barriers to psychological treatments and their relationship to depression. *Journal of clinical psychology*, *66*(4), 394-409.

Mojtabai, R., Olfson, M., Sampson, N. A., Jin, R., Druss, B., Wang, P. S., . . . Kessler, R. C. (2011). Barriers to Mental Health Treatment: Results from the National Comorbidity Survey Replication (NCS-R). *Psychological medicine*, *41*(8), 1751-1761.

Moritz, S., Schilling, L., Hauschildt, M., Schröder, J., & Treszl, A. (2012). A randomized controlled trial of internet-based therapy in depression. *Behaviour research and therapy*, *50*(7), 513-521.

Mossey, J. M., Knott, K. A., Higgins, M., & Talerico, K. (1996). Effectiveness of a psychosocial intervention, interpersonal counseling, for subdysthymic depression in medically ill elderly. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *51*(4), M172-M178.

Mukhtar, F. (2011). Predictors of group cognitive behaviour therapy outcomes for the treatment of depression in Malaysia. *Asian journal of psychiatry*, *4*(2), 125-128.

Munder, T., Brütsch, O., Leonhart, R., Gerger, H., & Barth, J. (2013). Researcher allegiance in psychotherapy outcome research: an overview of reviews. *Clinical psychology review*, *33*(4), 501-511.

Muñoz, R. F., Bunge, E. L., Chen, K., Schueller, S. M., Bravin, J. I., Shaughnessy, E. A., & Pérez-Stable, E. J. (2016). Massive open online interventions: A novel model for delivering behavioral-health services worldwide. *Clinical Psychological Science*, *4*(2), 194-205.

Musiat, P., Goldstone, P., & Tarrier, N. (2014). Understanding the acceptability of e-mental health-attitudes and expectations towards computerised self-help treatments for mental health problems. *BMC Psychiatry*, *14*(1), 109.

Mynors-Wallis, L. M., Gath, D. H., Day, A., & Baker, F. (2000). Randomised controlled trial of problem solving treatment, antidepressant medication, and combined treatment for major depression in primary care. *BMJ (Clinical research ed.)*, (7226), 26-30.

Naeem, F., Sarhandi, I., Gul, M., Khalid, M., Aslam, M., Anbrin, A., . . . Minhas, F. (2014). A multicentre randomised controlled trial of a carer supervised culturally adapted CBT (CaCBT) based self-help for depression in Pakistan. *Journal of affective disorders* , *156*, 224-227.

Nakimuli-Mpungu, E., Wamala, K., Okello, J., Alderman, S., Odokonyero, R., Mojtabai, R., . . . Musisi, S. (2015). Group support psychotherapy for depression treatment in people with HIV/AIDS in northern Uganda: A single-centre randomised controlled trial. *The Lancet HIV*, *2*(5), e190-e199.

National Collaborating Centre for Mental Health (UK. (2010). Depression: the treatment and management of depression in adults (updated edition). British Psychological Society.

National Collaborating Centre for Mental Health. (2010b). National Institute for Health and Clinical Excellence: Guidance *Depression: The Treatment and Management of Depression in Adults (Updated Edition)*. Leicester (UK): The British Psychological Society & The Royal College of Psychiatrists.

National Institute for Clinical Excellence. (2004). *Depression: management of depression in primary and secondary care*. London: National Institute for Clinical Excellence.

Newby, J. M., Mackenzie, A., Williams, A. D., McIntyre, K., Watts, S., Wong, N., & Andrews, G. (2013). Internet cognitive behavioural therapy for mixed anxiety and depression: a randomized controlled trial and evidence of effectiveness in primary care. *Psychological medicine*, *43*(12), 2635-2648.

Newman, M. G. (2000). Recommendations for a cost-offset model of psychotherapy allocation using generalized anxiety disorder as an example. *Journal of consulting and clinical psychology*, *68*(4), 549.

Newman, M. G., Erickson, T., Przeworski, A., & Dzus, E. (2003). Self-help and minimal-contact therapies for anxiety disorders: Is human contact necessary for therapeutic efficacy? *Journal of clinical psychology*, *59*(3), 251-274.

Newton-Howes, G., Tyrer, P., & Johnson, T. (2006). Personality disorder and the outcome of depression: meta-analysis of published studies. *The British Journal of Psychiatry*, *188*(1), 13-20.

Ng, S., Tien, A., Thayala, J. N., Ho, R., & Chan, M. (2013). The effect of life story review on depression of older communityβdwelling Chinese adults in Singapore: a preliminary result. *International journal of geriatric psychiatry*, *28*(3), 328-330.

Ngai, F. W., Wong, P.-C., Leung, K. Y., Chau, P. H., & Chung, K. F. (2015). The effect of telephone-based cognitive-behavioral therapy on postnatal depression: A randomized controlled trial. *Psychotherapy and psychosomatics*, *84*(5), 294-303.

Nobis, S., Lehr, D., Ebert, D. D., Baumeister, H., Snoek, F., Riper, H., & Berking, M. (2015). Efficacy of a web-based intervention with mobile phone support in treating depressive symptoms in adults with type 1 and type 2 diabetes: A randomized controlled trial. *Diabetes Care*, *38*(5), 776-783.

Nobis, S., Lehr, D., Ebert, D. D., Berking, M., Heber, E., Baumeister, H., . . . Riper, H. (2013). Efficacy and cost-effectiveness of a web-based intervention with mobile phone support to treat depressive symptoms in adults with diabetes mellitus type 1 and type 2: design of a randomised controlled trial. *BMC Psychiatry*, *13*(1), 306.

Nock, M. K., Hwang, I., Sampson, N., Kessler, R. C., Angermeyer, M., Beautrais, A., . . . Williams, D. R. (2009). Cross-National Analysis of the Associations among Mental Disorders and Suicidal Behavior: Findings from the WHO World Mental Health Surveys. *PLoS Med*, *6*(8), e1000123.

Ogrodniczuk, J. S., Piper, W. E., & Joyce, A. S. (2004). Residual symptoms in depressed patients who successfully respond to short-term psychotherapy. *Journal of affective disorders*, *82*(3), 469-473.

O'Mahen, H., Himle, J. A., Fedock, G., Henshaw, E., & Flynn, H. (2013). A pilot randomized controlled trial of cognitive behavioral therapy for perinatal depression adapted for women with low incomes. *Depress Anxiety*, *30*(7), 679-687.

Omidi, A., Mohammadkhani, P., Mohammadi, A., & Zargar, F. (2013). Comparing mindfulness based cognitive therapy and traditional cognitive behavior therapy with treatments as usual on reduction of major depressive disorder symptoms. *Iranian Red Crescent Medical Journal*, *15*(2), 142-146.

Organisation for Economic Cooperation and Development, O. (2016a). OECD Consumer Price Index. Retrieved March 10, 2016, from https://data.oecd.org/price/inflation-cpi.htm.

Organisation for Economic Cooperation and Development, O. (2016b). OECD Purchasing Power Parities for private consumption. Retrieved March 10, 2016, from http://stats.oecd.org/Index.aspx?DataSetCode=SNA_TABLE4.

Ormel, J., Petukhova, M., Chatterji, S., Aguilar-Gaxiola, S., Alonso, J., Angermeyer, M. C., . . . Kessler, R. C. (2008). Disability and treatment of specific mental and physical disorders across the world. *The British Journal of Psychiatry*, *192*(5), 368-375.

Orsini, N., Bottai, M., Higgins, J., & Buchan, I. (2006). Heterogi: Stata module to quantify heterogeneity in a meta-analysis. *Statistical Software Components*.

Pagoto, S., Schneider, K. L., Whited, M. C., Oleski, J. L., Merriam, P., Appelhans, B., ... & Lemon, S. (2013). Randomized controlled trial of behavioral treatment for comorbid obesity and depression in women: the Be Active Trial. *International journal of obesity (2005)*, *37*(11), 1427.

Pampallona, S., Bollini, P., Tibaldi, G., Kupelnick, B., & Munizza, C. (2004). Combined pharmacotherapy and psychological treatment for depression: a systematic review. *Archives of general psychiatry*, *61*(7), 714-719.

Parikh, S. V., Segal, Z. V., Grigoriadis, S., Ravindran, A. V., Kennedy, S. H., Lam, R. W., & Patten, S. B. (2009). Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. II. Psychotherapy alone or in combination with antidepressant medication. *Journal of affective disorders*, *117 Suppl 1*, S15-25.

Paykel, E. S., Scott, J., Teasdale, J. D., Johnson, A. L., Garland, A., Moore, R., … Pope, M. (1999). Prevention of relapse in residual depression by cognitive therapy: a controlled trial. *Archives of general psychiatry*, (9), 829-835.

Perini, S., Titov, N., & Andrews, G. (2009). Clinician-assisted Internet-based treatment is effective for depression: randomized controlled trial. *Australian and New Zealand journal of psychiatry*, *43*(6), 571-578.

Perlis, R. H., Nierenberg, A. A., Alpert, J. E., Pava, J., Matthews, J. D., Buchin, J., … Fava, M. (2002). Effects of adding cognitive therapy to fluoxetine dose increase on risk of relapse and residual depressive symptoms in continuation treatment of major depressive disorder. *Journal of Clinical Psychopharmacol*, *22*(5), 474-480.

Petersen, I., Hanass Hancock, J., Bhana, A., & Govender, K. (2014). A group-based counselling intervention for depression comorbid with HIV/AIDS using a task shifting approach in South Africa: A randomized controlled pilot study. *Journal of Affective Disorders*, *158*, 78-84.

Phillips, R., Schneider, J., Molosankwe, I., Leese, M., Foroushani, P. S., Grime, P., … Thornicroft, G. (2014). Randomized controlled trial of computerized cognitive behavioural therapy for depressive symptoms: effectiveness and costs of a workplace intervention. *Psycholological Medicine*, *44*(4), 741-752.

Piet, J., & Hougaard, E. (2011). The effect of mindfulness-based cognitive therapy for prevention of relapse in recurrent major depressive disorder: a systematic review and meta-analysis. *Clinical psychology review*, *31*(6), 1032-1040.

Pizzi, C., Rutjes, A. W. S., Costa, G. M., Fontana, F., Mezzetti, A., & Manzoli, L. (2011). Meta-analysis of selective serotonin reuptake inhibitors in patients with depression and coronary heart disease. *American Journal of Cardiology*, *107*(7), 972-979.

Poleshuck, E. L., Gamble, S. A., Bellenger, K., Lu, N., Tu, X., Sörensen, S., … Talbot, N. L. (2014). Randomized controlled trial of interpersonal psychotherapy versus enhanced treatment as usual for women with co-occurring depression and pelvic pain. *Journal of psychosomatic research*, *77*(4), 264-272.

Power, M. J., & Freeman, C. (2012). A randomized controlled trial of IPT versus CBT in primary care: With some cautionary notes about handling missing values in clinical trials. *Clinical psychology & psychotherapy*, *19*(2), 159-169.

Prendergast, J., & Austin, M. P. (2001). Early childhood nurse-delivered cognitive behavioural counselling for post-natal depression. *Australasian Psychiatry*, (3), 255-259.

Qaseem, A., Barry, M. J., & Kansagara, D. (2016). Nonpharmacologic versus pharmacologic treatment of adult patients with major depressive disorder: a clinical practice guideline from the American College of Physicians. *Annals of Internal Medicine*, *164*(5), 350-359.

Qiu, J., Chen, W., Gao, X., Xu, Y., Tong, H., Yeng, M., . . . Yang, M. (2013). A randomized controlled trial of group cognitive behavioral therapy for Chinese breast cancer patients with major depression. *Journal of Psychosomatic Obstetrics and Gynecology*, *34*(2), 60-67.

Rabheru, K. (2012). Maintenance electroconvulsive therapy (M-ECT) after acute response: examining the evidence for who, what, when, and how?. *The journal of ECT*, *28*(1), 39-47.

Radloff, L. S. (1977). The CES-D scale a self-report depression scale for research in the general population. *Applied psychological measurement*, *1*(3), 385-401.

Rahman, A., Malik, A., Sikander, S., Roberts, C., & Creed, F. (2008). Cognitive behaviour therapy-based intervention by community health workers for mothers with depression and their infants in rural Pakistan: A cluster-randomised controlled trial. *The Lancet*, *372*(9642), 902-909.

Rapaport, M. H., Clary, C., Fayyad, R., & Endicott, J. (2005). Quality-of-life impairment in depressive and anxiety disorders. *American journal of psychiatry*, *162*(6), 1171-1178.

Reddy, M. (2010). Depression: the disorder and the burden. *Indian journal of psychological medicine*, *32*(1), 1.

Reddy, M. S. (2010). Depression: The Disorder and the Burden. *Indian Journal of Psychological Medicine*, *32*(1), 1-2.

Revicki, D. A., Siddique, J., Frank, L., Chung, J. Y., Green, B. L., Krupnick, J., . . . Miranda, J. (2005). Cost-effectiveness of evidence-based pharmacotherapy or cognitive behavior therapy compared with community referral for major depression in predominantly low-income minority women. *Archives of general psychiatry*, *62*(8), 868-875.

Reynolds Iii, C. F., Dew, M. A., Pollock, B. G., Mulsant, B. H., Frank, E., Miller, M. D., . . . Kupfer, D. J. (2006). Maintenance treatment of major depression in old age. *New England Journal of Medicine*, *354*(11), 1130-1138.

Reynolds, C. F., 3rd, Frank, E., Dew, M. A., Houck, P. R., Miller, M., Mazumdar, S., . . . Kupfer, D. J. (1999). Treatment of 70(+)-year-olds with recurrent major depression. Excellent short-term but brittle long-term response. *The American journal of geriatric psychiatry*, *7*(1), 64-69.

Richards, D., & Richardson, T. (2012). Computer-based psychological treatments for depression: a systematic review and meta-analysis. *Clin Psychol Rev*, *32*(4), 329-342.

Riley, R. D., Lambert, P. C., & Abo-Zaid, G. (2010). Meta-analysis of individual participant data: rationale, conduct, and reporting. *Bmj*, *340*, c221.

Riley, R. D., Simmonds, M. C., & Look, M. P. (2007). Evidence synthesis combining individual patient data and aggregate data: a systematic review identified current practice and possible methods. *Journal of clinical epidemiology*, *60*(5), 431-439.

Riso, L. P., Thase, M. E., Howland, R. H., Friedman, E. S., Simons, A. D., & Tu, X. M. (1997). A prospective test of criteria for response, remission, relapse, recovery, and recurrence in depressed patients treated with cognitive behavior therapy. *Journal of affective disorders*, *43*(2), 131-142.

Robinson, T. N., Patrick, K., Eng, T. R., & Gustafson, D. (1998). An evidence-based approach to interactive health communication: a challenge to medicine in the information age. *Jama*, *280*(14), 1264-1269.

Rosenthal, J. A. (1996). Qualitative descriptors of strength of association and effect size. *Journal of social service Research*, *21*(4), 37-59.

Rozental, A., Andersson, G., Boettcher, J., Ebert, D. D., Cuijpers, P., Knaevelsrud, C., . . . Carlbring, P. (2014). Consensus statement on defining and measuring negative effects of Internet interventions. *Internet Interventions*, *1*(1), 12-19.

Rubin, D. B. (2004). *Multiple imputation for nonresponse in surveys* (Vol. 81). New York: John Wiley & Sons.

Rush, A. J., Kraemer, H. C., Sackeim, H. A., Fava, M., Trivedi, M. H., Frank, E., . . . Kupfer, D. J. (2006). Report by the ACNP Task Force on response and remission in major depressive disorder. *Neuropsychopharmacology*, *31*(9), 1841-1853.

Ruwaard, J., Schrieken, B., Schrijver, M., Broeksteeg, J., Dekker, J., Vermeulen, H., & Lange, A. (2009). Standardized web-based cognitive behavioural therapy of mild to moderate depression: a randomized controlled trial with a long-term follow-up. *Cogn Behav Ther*, *38*(4), 206-221.

Saarni, S. I., Suvisaari, J., Sintonen, H., Pirkola, S., Koskinen, S., Aromaa, A., & LÖNNQVIST, J. (2007). Impact of psychiatric disorders on health-related quality of life: general population survey. *The British Journal of Psychiatry*, *190*(4), 326-332.

Sareen, J., Jagdeo, A., Cox, B. J., Clara, I., ten Have, M., Belik, S. L., ... & Stein, M. B. (2007). Perceived barriers to mental health service utilization in the United States, Ontario, and the Netherlands. *Psychiatric services*, *58*(3), 357-364.

Sava, F. A., Yates, B. T., Lupu, V., Szentagotai, A., & David, D. (2009). Costβeffectiveness and costβutility of cognitive therapy, rational emotive behavioral therapy, and fluoxetine (prozac) in treating depression: a randomized clinical trial. *Journal of clinical psychology*, *65*(1), 36-52.

Schene, A. H., Koeter, M. W., Kikkert, M. J., Swinkels, J. A., & McCrone, P. (2007). Adjuvant occupational therapy for work-related major depression works: randomized trial including economic evaluation. *Psychological Medicine*, *37*(3), 351-362.

Schramm, E., van Calker, D., Dykierek, P., Lieb, K., Kech, S., Zobel, I., . . . Berger, M. (2007). An intensive treatment program of interpersonal psychotherapy plus pharmacotherapy for depressed inpatients: acute and long-term results. *American journal of psychiatry*, *164*(5), 768-777.

Schröder, J., Brückner, K., Fischer, A., Lindenau, M., Köther, U., Vettorazzi, E., & Moritz, S. (2014). Efficacy of a psychological online intervention for depression in people with epilepsy: a randomized controlled trial. *Epilepsia*, *55*(12), 2069-2076.

Schroder, J., Sautier, L., Kriston, L., Berger, T., Meyer, B., Spath, C., . . . Moritz, S. (2015). Development of a questionnaire measuring Attitudes towards Psychological Online Interventions-the APOI. *Journal of affective disorders*, *187*, 136-141.

Scott, C., Tacchi, M. J., Jones, R., & Scott, J. (1997). Acute and one-year outcome of a randomised controlled trial of brief cognitive therapy for major depressive disorder in primary care. *The British journal of psychiatry : the journal of mental science*, 131-134.

Scott, K., Bruffaerts, R., Tsang, A., Ormel, J., Alonso, J., Angermeyer, M., . . . De Graaf, R. (2007). Depression–anxiety relationships with chronic physical conditions: results from the World Mental Health Surveys. *Journal of affective disorders*, *103*(1), 113-120.

Serfaty, M. A., Deborah, H., Buszewicz, M., Blanchard, M., Murad, S., & King, M. (2011). The clinical effectiveness of individual cognitive behaviour therapy for depressed older people in primary care and the use of a talking control (TC). *European Psychiatry*, *26*.

Serfaty, M. A., Haworth, D., Blanchard, M., Buszewicz, M., Murad, S., & King, M. (2009). Clinical effectiveness of individual cognitive behavioral therapy for depressed older people in primary care: a randomized controlled trial. *Archives of General Psychiatry*, (12), 1332-1340.

Shea, M. T., Elkin, I., Imber, S. D., Sotsky, S. M., Watkins, J. T., Collins, J. F., . . . et al. (1992). Course of depressive symptoms over follow-up. Findings from the National Institute of Mental Health Treatment of Depression Collaborative Research Program. *Arch Gen Psychiatry*, *49*(10), 782-787.

Sheeber, L. B., Seeley, J. R., Feil, E. G., Davis, B., Sorensen, E., Kosty, D. B., & Lewinsohn, P. M. (2012). Development and pilot evaluation of an Internet-facilitated cognitive-behavioral intervention for maternal depression. *Journal of consulting and clinical psychology*, *80*(5), 739.

Shimodera, S., Furukawa, T. A., Mino, Y., Shimazu, K., Nishida, A., & Inoue, S. (2012). Cost-effectiveness of family psychoeducation to prevent relapse in major depression: results from a randomized controlled trial. *BMC Psychiatry*, *12*, 40.

Siev, J., & Chambless, D. L. (2007). Specificity of treatment effects: Cognitive therapy and relaxation for generalized anxiety and panic disorders: American Psychological Association.

Siev, J., Huppert, J. D., & Chambless, D. L. (2009). The Dodo Bird, treatment technique, and disseminating empirically supported treatments. *The Behavior Therapist*.

Simons, A. D., Murphy, G. E., Levine, J. L., & Wetzel, R. D. (1986). Cognitive therapy and pharmacotherapy for depression. Sustained improvement over one year. *Archives of general psychiatry*, *43*(1), 43-48.

Simpson, S., Corney, R., & Beecham, J. (2003). A randomized controlled trial to evaluate the effectiveness and cost-effectiveness of psychodynamic counselling for general practice patients with chronic depression. *Psychological Medicine*, *33*(2), 229-239.

Sirey, J. A., Bruce, M. L., & Alexopoulos, G. S. (2005). The Treatment Initiation Program: an intervention to improve depression outcomes in older adults. *American journal of psychiatry*, *162*(1), 184-186.

Smit, A., Kluiter, H., Conradi, H. J., van der Meer, K., Tiemens, B. G., Jenner, J. A., . . . Ormel, J. (2006). Short-term effects of enhanced treatment for depression in primary care: results from a randomized controlled trial. *Psychological Medicine*, *36*(1), 15-26.

Smit, F., Comijs, H., Schoevers, R., Cuijpers, P., Deeg, D., & Beekman, A. (2007). Target groups for the prevention of late-life anxiety. *British journal of psychiatry*, *190*, 428-434.

Smit, F., Cuijpers, P., Oostenbrink, J., Batelaan, N., de Graaf, R., & Beekman, A. (2006). Costs of nine common mental disorders: implications for curative and preventive psychiatry. *Journal of Mental Health Policy and Economics*.

Smith, K. L., Matheson, F. I., Moineddin, R., Dunn, J. R., Lu, H., Cairney, J., & Glazier, R. H. (2013). Gender differences in mental health service utilization among respondents reporting depression in a national health survey. *Health*, *5*(10), 1561.

Songprakun, W., & McCann, T. V. (2012). Evaluation of a cognitive behavioural selfβhelp manual for reducing depression: a randomized controlled trial. *Journal of psychiatric and mental health nursing*, *19*(7), 647-653.

Spek, V., Cuijpers, P., Nyklícek, I., Riper, H., Keyzer, J., & Pop, V. (2007). Internet-based cognitive behaviour therapy for symptoms of depression and anxiety: a meta-analysis. *Psychological medicine*, *37*(03), 319-328.

Spek, V., Nyklicek, I., Cuijpers, P., & Pop, V. (2008). Predictors of outcome of group and internet-based cognitive behavior therapy. *Journal of affective disorders*, *105*(1-3), 137-145.

Spek, V., Nyklíβek, I., Smits, N., Cuijpers, P., Riper, H., Keyzer, J., & Pop, V. (2007). Internet-based cognitive behavioural therapy for subthreshold depression in people over 50 years old: a randomized controlled clinical trial. *Psychological medicine*, *37*(12), 1797-1806.

Spijker, J., Bijl, R. V., De Graaf, R., & Nolen, W. A. (2001). Care utilization and outcome of DSMβIIIβR major depression in the general population. Results from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Acta Psychiatrica Scandinavica*, *104*(1), 19-24.

Sreevani, R., Reddemma, K., Chan, C. L., Leung, P. P., Wong, V., & Chan, C. H. (2013). Effectiveness of integrated body-mind-spirit group intervention on the well-being of Indian patients with depression: A pilot study. *Journal of Nursing Research*, *21*(3), 179-186.

Stant, A. D., ten Vergert, E. M., Kluiter, H., Conradi, H. J., Smit, A., & Ormel, J. (2009). Cost-effectiveness of a psychoeducational relapse prevention program for depression in primary care. *The journal of mental health policy and economics*, *12*(4), 195-204.

Stata Statistical Software: Release 13. (2015). College Station: StataCorp LP.

StataCorp. (2011). Stata Statistical Software: Release 12.College Station: StataCorp LP.

Steel, Z., Marnane, C., Iranpour, C., Chey, T., Jackson, J. W., Patel, V., & Silove, D. (2014). The global prevalence of common mental disorders: a systematic review and meta-analysis 1980–2013. *International journal of epidemiology*, *43*(2), 476-493.

Stewart, L. A., Clarke, M., Rovers, M., Riley, R. D., Simmonds, M., Stewart, G., & Tierney, J. F. (2015). Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. *Jama*, *313*(16), 1657-1665.

Stewart, L., & Parmar, M. (1993). Meta-analysis of the literature or of individual patient data: is there a difference? *The Lancet*, *341*(8842), 418-422.

Swartz, H. A., Frank, E., Zuckoff, A., Cyranowski, J. M., Houck, P. R., Cheng, Y., . . . Shear, M. K. (2008). Brief interpersonal psychotherapy for depressed mothers whose children are receiving psychiatric treatment. *American journal of psychiatry*, *165*(9), 1155-1162.

Tandon, S. D., Leis, J. A., Mendelson, T., Perry, D. F., & Kemp, K. (2014). Six-month outcomes from a randomized controlled trial to prevent perinatal depression in low-income home visiting clients. *Maternal and child health journal*, *18*(4), 873-881.

Taylor, D. J., Walters, H. M., Vittengl, J. R., Krebaum, S., & Jarrett, R. B. (2010). Which depressive symptoms remain after response to cognitive therapy of depression and predict relapse and recurrence? *Journal of affective disorders*, *123*(1), 181-187.

Teasdale, J. D., Fennell, M. J., Hibbert, G. A., & Amies, P. L. (1984). Cognitive therapy for major depressive disorder in primary care. *British journal of psychiatry*, *144*, 400-406.

Teichman, Y., Bar-el, Z., Shor, H., Sirota, P., & Elizur, A. (1995). A comparison of two modalities of cognitive therapy (individual and marital) in treating depression. *Psychiatry*, *58*(2), 136-148.

Thase, M., & Ninan, P. (2001). New goals in the treatment of depression: moving toward recovery. *Psychopharmacology bulletin*, *36*, 24-35.

Titov, N. (2011). Internet-delivered psychotherapy for depression in adults. *Current opinion in psychiatry*, *24*(1), 18-23.

Titov, N., Andrews, G., Davies, M., McIntyre, K., Robinson, E., & Solley, K. (2010). Internet treatment for depression: a randomized controlled trial comparing clinician vs. technician assistance. *PLoS One*, *5*(6), e10939.

Titov, N., Dear, B. F., Ali, S., Zou, J. B., Lorian, C. N., Johnston, L., . . . Gandy, M. (2015). Clinical and cost-effectiveness of therapist-guided internet-delivered cognitive behavior therapy for older adults with symptoms of depression: a randomized controlled trial. *Behavior therapy*, *46*(2), 193-205.

Titov, N., Dear, B. F., Schwencke, G., Andrews, G., Johnston, L., Craske, M. G., & McEvoy, P. (2011). Transdiagnostic internet treatment for anxiety and depression: a randomised controlled trial. *Behaviour research and therapy*, *49*(8), 441-452.

Tordrup, D., & Bertollini, R. (2014). Consolidated research agenda needed for health economic evaluation in Europe. *Bmj*, *349*, g5228.

Tordrup, D., Attwill, A., Crosby, L., & Bertollini, R. (2015). Research Agenda for Health Economic Evaluation - Expert Meeting Report.

Turner, D. T., van der Gaag, M., Karyotaki, E., & Cuijpers, P. (2014). Psychological interventions for psychosis: a meta-analysis of comparative outcome studies. *American journal of psychiatry*, *171*(5), 523-538.

Turner, E. H., Matthews, A. M., Linardatos, E., Tell, R. A., & Rosenthal, R. (2008). Selective publication of antidepressant trials and its influence on apparent efficacy. *New England Journal of Medicine*, *358*(3), 252-260.

Unlu Ince, B., Cuijpers, P., t Hof, E., Ballegooijen, W., Christensen, H., & Riper, H. (2013). Internet-based, culturally sensitive, problem-solving therapy for Turkish migrants with depression: Randomized controlled trial. *Journal of medical Internet research*, *15*(10), e227.

Üstün, T. B., Ayuso-Mateos, J. L., Chatterji, S., Mathers, C., & Murray, C. J. L. (2004). Global burden of depressive disorders in the year 2000. *The British Journal of Psychiatry*, *184*(5), 386-392.

van Ballegooijen, W., Cuijpers, P., van Straten, A., Karyotaki, E., Andersson, G., Smit, J. H., & Riper, H. (2014). Adherence to Internet-based and face-to-face cognitive behavioural therapy for depression: a meta-analysis. *PLoS One*, *9*(7), e100674.

van Bastelaar, K. M., Pouwer, F., Cuijpers, P., Riper, H., & Snoek, F. J. (2011). Web-based depression treatment for type 1 and type 2 diabetic patients: A randomized, controlled trial. *Diabetes Care*, *34*(2), 320-325.

van Schaik, A., van Marwijk, H., Adèr, H., van Dyck, R., de Haan, M., Penninx, B., . . . Beekman, A. (2006). Interpersonal psychotherapy for elderly patients in primary care. *The American Journal of Geriatric Psychiatry*, *14*(9), 777-786.

van Schaik, D. J., Klijn, A. F., van Hout, H. P., van Marwijk, H. W., Beekman, A. T., de Haan, M., & van Dyck, R. (2004). Patients' preferences in the treatment of depressive disorder in primary care. *General hospital psychiatry*, *26*(3), 184-189.

van Straten, A., Hill, J., Richards, D., & Cuijpers, P. (2015). Stepped care treatment delivery for depression: a systematic review and meta-analysis. *Psychological medicine*, *45*(02), 231-246.

Vaughan, B., Goldstein, M. H., Alikakos, M., Cohen, L. J., & Serby, M. J. (2014). Frequency of reporting of adverse events in randomized controlled trials of psychotherapy vs. psychopharmacotherapy. *Comprehensive psychiatry*, *55*(4), 849-855.

Verduyn, C., Barrowclough, C., Roberts, J., Tarrier, N., & Harrington, R. (2003). Maternal depression and child behaviour problems Randomised placebo-controlled trial of a cognitive-behavioural group intervention. *British Journal of Psychiatry*, *183*(OCT.), 342-348.

Vernmark, K., Lenndin, J., Bjärehed, J., Carlsson, M., Karlsson, J., Öberg, J., ... & Andersson, G. (2010). Internet administered guided self-help versus individualized e-mail therapy: A randomized trial of two versions of CBT for major depression. *Behaviour research and therapy*, *48*(5), 368-376.

Vitriol, V. G., Ballesteros, S. T., Florenzano, R. U., Weil, K. P., & Benadof, D. F. (2009). Evaluation of an outpatient intervention for women with severe depression and a history of childhood trauma. *Psychiatric Services*, *60*(7), 936-942.

Wade, A. G., Fern·ndez, J. L., FranÁois, C., Hansen, K., Danchenko, N., & Despiegel, N. (2008). Escitalopram and duloxetine in major depressive disorder: a pharmacoeconomic comparison using UK cost data. *Pharmacoeconomics*, *26*(11), 969-981.

Waller, R., & Gilbody, S. (2009). Barriers to the uptake of computerized cognitive behavioural therapy: a systematic review of the quantitative and qualitative evidence. *Psychological medicine*, *39*(05), 705-712.

Wang, P. S., Gruber, M. J., Powers, R. E., Schoenbaum, M., Speier, A. H., Wells, K. B., & Kessler, R. C. (2007). Mental health service use among Hurricane Katrina survivors in the eight months after the disaster. *Psychiatric services*, *58*(11), 1403-1411.

Wang, P. S., Lane, M., Olfson, M., Pincus, H. A., Wells, K. B., & Kessler, R. C. (2005). Twelve-month use of mental health services in the United States: results from the National Comorbidity Survey Replication. *Archives of general psychiatry*, *62*(6), 629-640.

Wang, P. S., Simon, G., & Kessler, R. C. (2003). The economic burden of depression and the costβeffectiveness of treatment. *International journal of methods in psychiatric research*, *12*(1), 22-33.

Waraich, P., Goldner, E. M., Somers, J. M., & Hsu, L. (2004). Prevalence and incidence studies of mood disorders: a systematic review of the literature. *The Canadian Journal of Psychiatry*, *49*(2), 124-138.

Warmerdam, L., Smit, F., van Straten, A., Riper, H., & Cuijpers, P. (2010). Cost-utility and cost-effectiveness of internet-based treatment for adults with depressive symptoms: randomized trial. *Journal of medical Internet Research*, *12*(5).

Warmerdam, L., Straten, A., Twisk, J., Riper, H., & Cuijpers, P. (2008). Internet-based treatment for adults with depressive symptoms: randomized controlled trial. *Journal of medical Internet Research*, *10*(4), e44.

Warmerdam, L., Van Straten, A., Twisk, J., & Cuijpers, P. (2013). Predicting outcome of Internet-based treatment for depressive symptoms. *Psychotherapy Research*, *23*(5), 559-567.

Weinmann, S., & Koesters, M. (2016). Mental health service provision in low and middle-income countries: recent developments. *Current opinion in psychiatry*, *29*(4), 270-275.

Weitz, E. S., Hollon, S. D., Twisk, J., van Straten, A., Huibers, M. J., David, D., ... Cristea, I. A. (2015). Baseline depression severity as moderator of depression outcomes between cognitive behavioral therapy vs pharmacotherapy: an individual patient data meta-analysis. *JAMA Psychiatry*, *72*(11), 1102-1109.

Whiteford, H., Harris, M., McKeon, G., Baxter, A., Pennell, C., Barendregt, J., & Wang, J. (2013). Estimating remission from untreated major depression: a systematic review and meta-analysis. *Psychological medicine*, *43*(08), 1569-1585.

Wiles, N., Thomas, L., Abel, A., Ridgway, N., Turner, N., Campbell, J., . . . Lewis, G. (2013). Cognitive behavioural therapy as an adjunct to pharmacotherapy for primary care based patients with treatment resistant depression: Results of the CoBalT randomised controlled trial. *The Lancet*, *381*(9864), 375-384.

Wilkinson, P., Alder, N., Juszczak, E., Matthews, H., Merritt, C., Montgomery, H., . . . Jacoby, R. (2009). A pilot randomised controlled trial of a brief cognitive behavioural group intervention to reduce recurrence rates in late life depression. *International Journal of Geriatric Psychiatry*, (1), 68-75.

Williams, A. D., Blackwell, S. E., Mackenzie, A., Holmes, E. A., & Andrews, G. (2013). Combining imagination and reason in the treatment of depression: a randomized controlled trial of internet-based cognitive-bias modification and internet-CBT for depression. *Journal of consulting and clinical psychology*, *81*(5), 793 -799.

Williams, C., Wilson, P., Morrison, J., McMahon, A., Andrew, W., & Allan, L. (2013). Guided Self-Help Cognitive Behavioural Therapy for Depression in Primary Care: A randomised Controlled Trial. *PLoS One*, (1), e52735.

Williams, J. W., Mulrow, C. D., Chiquette, E., Noël, P. H., Aguilar, C., & Cornell, J. (2000). A systematic review of newer pharmacotherapies for depression in adults: evidence report summary: clinical guideline, part 2. *Annals of internal medicine*, *132*(9), 743-756.

Winter, S. E., & Barber, J. P. (2013). Should treatment for depression be based more on patient preference? *Patient preference and adherence*, *7*, 1047.

Wittchen, H. U., Jacobi, F., Rehm, J., Gustavsson, A., Svensson, M., Jönsson, B., . . . Steinhausen, H. C. (2011). The size and burden of mental disorders and other disorders of the brain in Europe 2010. *European Neuropsychopharmacology*, *21*(9), 655-679.

Wittchen, H.-U., Jacobi, F., Rehm, J., Gustavsson, A., Svensson, M., Jönsson, B., . . . Faravelli, C. (2011). The size and burden of mental disorders and other disorders of the brain in Europe 2010. *European Neuropsychopharmacology*, *21*(9), 655-679.

Wong, D. F. (2008a). Cognitive and health-related outcomes of group cognitive behavioural treatment for people with depressive symptoms in Hong Kong: Randomized wait-list control study. *Australian and New Zealand Journal of Psychiatry*, *42*(8), 702-711.

Wong, D. F. (2008b). Cognitive behavioral treatment groups for people with chronic depression in Hong Kong: A randomized wait-list control design. *Depression and Anxiety*, *25*(2), 142-148.

World Bank, W. (2015). Inflation, consumer prices. Retrieved 15 March 2016 from http://data.worldbank.org/indicator/ FP.CPI.TOTL.ZG/countries/RO?display=default.

World Health Organization. (2001). The World Health Report 2001: Mental health: new understanding, new hope: World Health Organization.

World Health Organization. (2010). WHO-AIMS: Mental Health Systems in Selected Low-and Middle-income Countries: a WHO-AIMS Cross-national Analysis: World Health Organization.

Ybarra, M. L., & Eaton, W. W. (2005). Internet-based mental health interventions. *Mental health services research*, *7*(2), 75-87.

Yin, P., & Fan, X. (2000). Assessing the reliability of Beck Depression Inventory scores: Reliability generalization across studies. *Educational and Psychological Measurement*, *60*(2), 201-223.

Zou, G. (2004). A modified poisson regression approach to prospective studies with binary data. *American journal of epidemiology*, *159*(7), 702-706.

Zu, S., Xiang, Y. T., Liu, J., Zhang, L., Wang, G., Ma, X., ... & Wong, S. Y. (2014). A comparison of cognitive-behavioral therapy, antidepressants, their combination and standard treatment for Chinese patients with moderate–severe major depressive disorders. *Journal of affective disorders*, *152*, 262-267.

APPENDICES

APPENDIX A

SEARCH STRINGS FOR PUBMED (CHAPTERS 2-4 & 6-10)

(Psychotherapy [MH] OR psychotherap*[All Fields] OR cbt[All Fields] OR "behavior therapies"[All Fields] OR "behavior therapy"[All Fields] OR "behavior therapeutic"[All Fields] OR "behavior therapeutical"[All Fields] OR "behavior therapeutics"[All Fields] OR "behavior therapeutist"[all Fields] OR "behavior therapeutists"[All Fields] OR "behavior treatment"[All Fields] OR "behavior treatments"[All Fields] OR "behaviors therapies"[All Fields] OR "behaviors therapy"[All Fields] OR "behaviors therapeutics"[All Fields] OR "behaviors therapeutic"[All Fields] OR "behaviors therapeutical"[All Fields] OR "behaviors therapeutist"[All Fields] OR "behaviors therapeutists"[All Fields] OR "behaviors treatment"[All Fields] OR "behaviors treatments"[All Fields] OR "behavioral therapies"[All Fields] OR "behavioral therapy"[All Fields] OR "behavioral therapeutics"[All Fields] OR "behavioral therapeutic"[All Fields] OR "behavioral therapeutical"[All Fields] OR "behavioral therapeutist"[All Fields] OR "behavioral therapeutists"[All Fields] OR "behavioral treatment"[All Fields] OR "behavioral treatments"[All Fields] OR "behaviour therapies"[All Fields] OR "behaviour therapy"[All Fields] OR "behaviour therapeutic"[All Fields] OR "behaviour therapeutical"[All Fields] OR "behaviour therapeutics"[All Fields] OR "behaviour therapeutist"[all Fields] OR "behaviour therapeutists"[All Fields] OR "behaviour treatment"[All Fields] OR "behaviour treatments"[All Fields] OR "behaviours therapies"[All Fields] OR "behaviours therapy"[All Fields] OR "behaviours therapeutics"[All Fields] OR "behaviours therapeutic"[All Fields] OR "behaviours therapeutical"[All Fields] OR "behaviours therapeutist"[All Fields] OR "behaviours therapeutists"[All Fields] OR "behaviours treatment"[All Fields] OR "behaviours treatments"[All Fields] OR "behavioural therapies"[All Fields] OR "behavioural therapy"[All Fields] OR "behavioural therapeutics"[All Fields] OR "behavioural therapeutic"[All Fields] OR "behavioural therapeutical"[All Fields] OR "behavioural therapeutist"[All Fields] OR "behavioural therapeutists"[All Fields] OR "behavioural treatment"[All Fields] OR "behavioural treatments"[All Fields] OR "cognition therapies"[All Fields] OR "cognition therapie"[All Fields] OR "cognition therapy"[All Fields] OR "cognition therapeutical"[All Fields] OR "cognition therapeutic"[All Fields] OR "cognition therapeutics"[All Fields] OR "cognition therapeutist"[All Fields] OR "cognition therapeutists"[All Fields] OR "cognition treatment"[All Fields] OR "cognition treatments"[All Fields] OR psychodynamic[All Fields] OR Psychoanalysis[MH] OR psychoanalysis[All Fields] OR psychoanalytic*[All Fields] OR counselling[All Fields] OR counseling[All Fields] OR Counseling[MH] OR "problem-solving"[All Fields] OR mindfulness[All Fields] OR (acceptance[All Fields] AND commitment[All Fields]) OR "assertiveness training"[All Fields] OR "behavior activation"[All Fields] OR "behaviors activation"[All Fields] OR "behavioral activation"[All Fields] OR "cognitive therapies"[All Fields] OR "cognitive therapy"[All Fields] OR "cognitive therapeutic"[All Fields] OR "cognitive therapeutics"[All Fields] OR "cognitive therapeutical"[All Fields] OR "cognitive therapeutist"[All Fields] OR "cognitive therapeutists"[All Fields] OR "cognitive treatment"[All Fields] OR "cognitive treatments"[All Fields] OR "cognitive restructuring"[All Fields] OR (("compassion-focused"[All Fields] OR "compassion-focussed"[All Fields]) AND (therapy[SH] OR therapies[All Fields] OR therapy[All Fields] OR therape*[All Fields] OR therapis*[All Fields]

OR Therapeutics [OR treatment*[All Fields])) OR ((therapy[SH] OR therapies[All Fields] OR therapy [All Fields] OR therape*[All Fields] OR therapis*[All Fields] OR Therapeutics[MH] OR treatment*[All Fields]) AND constructivist*[All Fields]) OR "metacognitive therapies"[All Fields] OR "metacognitive therapy"[All Fields] OR "metacognitive therapeutic"[All Fields] OR "metacognitive therapeutics"[All Fields] OR "metacognitive therapeutical"[All Fields] OR "metacognitive therapeutist"[All Fields] OR "metacognitive therapeutists"[All Fields] OR "metacognitive treatment"[All Fields] OR "metacognitive treatments"[All Fields] OR "meta-cognitive therapies"[All Fields] OR "meta-cognitive therapy"[All Fields] OR "meta-cognitive therapeutic"[All Fields] OR "meta-cognitive therapeutics"[All Fields] OR "meta-cognitive therapeutical"[All Fields] OR "meta-cognitive therapeutist"[All Fields] OR "meta-cognitive therapeutists"[All Fields] OR "meta-cognitive treatment"[All Fields] OR "meta-cognitive treatments"[All Fields] OR "solution-focused therapies"[All Fields] OR "solution-focused therapy"[All Fields] OR "solution-focused therapeutic"[All Fields] OR "solution-focused therapeutics"[All Fields] OR "solution-focused therapeutical"[All Fields] OR "solution focused therapies"[All Fields] OR "solution focused therapy"[All Fields] OR "solution focused therapeutic"[All Fields] OR "solution focused therapeutics"[All Fields] OR "solution focused therapeutical"[All Fields]OR "solution-focussed therapies"[All Fields] OR "solution-focussed therapy"[All Fields] OR "solution-focussed therapeutic"[All Fields] OR "solution-focussed therapeutics"[All Fields] OR "solution-focussed therapeutical"[All Fields]OR "solution focussed therapies"[All Fields] OR "solution focussed therapy"[All Fields] OR "solution focussed therapeutic"[All Fields] OR "solution focussed therapeutics"[All Fields] OR "solution focussed therapeutical"[All Fields] OR "self-control therapies"[All Fields] OR "self-control therapy"[All Fields] OR "self-control therapeutics"[All Fields] OR "self-control therapeutical"[All Fields] OR "self-control therapeutic"[All Fields] OR "self-control training"[All Fields] OR "self-control trainings"[All Fields] OR "self control therapies"[All Fields] OR "self control therapy"[All Fields] OR "self control therapeutics"[All Fields] OR "self control therapeutical"[All Fields] OR "self control therapeutic"[All Fields] OR "self control training"[All Fields] OR "self control trainings"[All Fields]

AND

(Depressive Disorder[MH] OR Depression[MH]OR dysthymi*[All Fields] OR "affective disorder"[All Fields]OR "affective disorders"[All Fields] OR "mood disorder"[All Fields] OR "mood disorders"[All Fields] OR depression*[All Fields] OR depressive*[All Fields] OR "dysthymic disorder"[MeSH Terms])

Limits: Randomized Controlled trials

SEARCH STRINGS FOR PUBMED (CHAPTER 5)

anxiety disorders[MH] OR anxiety disorders OR "gad" OR "generalized anxiety disorder" OR "generalised anxiety disorder" OR anxiety* OR "generalised anxiety" OR "worry" OR worry* OR Obsessive-Compulsive disorder[MH] OR "obsessive-compulsive" OR "ocd" OR "obsessive compulsive disorder" OR "obsessive compulsive" OR "social phobia" OR "social anxiety disorder" OR "social anxiety" OR stress disorders, post-traumatic[MH] OR "ptsd" OR "posttraumatic stress disorder" OR "posttraumatic stress" OR "post-traumatic stress" OR "acute stress disorder" OR "acute stress" OR panic disorder[MH] OR "panic disorder" OR "panic" OR agoraphobia[MH] OR "agorophobia" OR Depressive Disorder[MH] OR Depression[MH] OR dysthymi*[All Fields] OR "affective disorder"[All Fields]OR "affective disorders"[All Fields] OR "mood disorder"[All Fields] OR "mood disorders"[All Fields] OR depression*[All Fields] OR depressive*[All Fields] OR "dysthymic disorder"[MeSH Terms])

AND

costs and cost analysis[MH] OR economics[MH] OR "cost effectiveness analysis" OR "cost effectiveness" OR "economic aspect "OR "cost" OR "costs" OR "cost effective" OR "health care cost" OR health care economics and organizations[MH] OR "economic" OR "cost benefit" OR cost-benefit analysis[MH] OR "cost utility" OR economic evaluation

Limits: Randomized Controlled trials

APPENDIX B (CHAPTER 2)

B1. TABLES

Table a – Additional characteristics of the included RCTs: psychotherapy (acute phase) vs. control groups in adults with depression

Studies	N of PT sessions & exact duration	Out-of-protocol interval treatment	Control group – detailed explanation
Allart-van Dam et al. 2007	12 weekly; 2h/session	NR	No treatment/naturalistic FU
Bass et al 2006	16 weekly, 90min/session	Naturalistic follow up	TAU – local traditional healers or counseling services by local HIV/AIDS organizations
Beeber et al 2010	16 (11 weekly nurse-interpreter visits alternated with 5 -15m booster visit or telephone or telephone call)	NR	TAU – not specified 4
Burns et al. 2013	12 not specified if it was weekly	NR	TAU – appointments with midwifes & scans (a dating & anomaly scan)
Choi et al. 2013	6 – 60 min sessions	NR	Attention control – telephone support call
Cooper et al. 2003	NR	NR	TAU- GPs and health visitors
Cramer et al. 2011	12/10 consecutive weeks	NR	TAU – GPs; information booklet
Dowrick et al. 2000	6 12/2h over 8 weeks	NR	No treatment – no intervention from the research team
Duarte et al. 2009	NR	NR	TAU – offered in the dialysis unit
Dwight-Johnson et al. 2011	8 weekly sessions; 45-50 min	NR	Enhanced TAU – including ADM or referral to outside services.
Elkin 1989	16 week treatment conditions	Naturalistic follow up	Placebo & CM
Evans et al. 1995	8 weekly sessions; 1 h	NR	No treatment community crisis for single consultation (if needed)
Freedland et al. 2009	6	NR	Non standardized control
Gary et al. 2010	12 weekly; 50-60 min sessions	NR	TAU – GPs; mostly ADM
Geraedts, et al., 2014	12 weekly sessions, 1 h	NR	TAU - NS
Hamamci et al. 2006	6 weekly modules	NR	TAU –NS; participants we free to follow any treatment they wanted
Honey et al. 2002	11 weekly sessions; 1,5 h 11 weekly sessions; 3 h	NR	No treatment
Kay-Lambkin et al. 2009	8 weekly sessions	NR	TAU - NS
Kessler et al. 2009	10 sessions in sequence; 1 week apart 9 sessions in sequence; 1 week apart	NR	One manualized session (Brief advice to reduce alcohol consumption) & No further treatment

Continued

Table a – Additional characteristics of the included RCTs: psychotherapy (acute phase) vs. control groups in adults with depression (Continued)

Studies	N of PT sessions & exact duration	Out-of-protocol interval treatment	Control group – detailed explanation
King et al 2000	10 55m sessions/16 weeks	NR	WL
Laidlaw et al. 2008	12 weekly sessions	Naturalistic follow up	TAU – GPs, ADM but not psychotherapy
Lamers et al. 2010	17	NR	TAU – GPs, mainly physical treatment, ADM
Lustman et al. 1998	10	NR	TAU – mainly for their somatic illness. A small n of patients receive ADM (n=7) and one consulted a psychiatrist or psychologist
MacPherson, et al. 2013	10 weekly sessions	NR	Non specific ADM
Miranda et al. 2003	12 weekly sessions	NR	TAU - NS
Mohr et al. 2011	8 weekly sessions	NR	TAU – educated about depression and mental health treatment available in the community
Mossey et al. 1996	16 weekly sessions (40-50 min)	NR	TAU – low intensity psychological care
O'Mahen et al. 2013	10 weekly sessions (30-60 min)	NR	TAU – mental health related services
Pagoto et al. 2013	12	NR	TAU – regular car that occurs in all clinics; on site social worker, psychoeducation materials
Poleshuck et al. 2014	26 sessions (16 individual sessions & 10 weekly group sessions)	NR	LI
Power et al. 2012	8 sessions weekly or biweekly	NR	TAU – a care coordinator facilitated the referrals for psychotherapy
Prendergast et al 2001	16 sessions	NR	TAU – GPs, normal clinical management (ADM)
Qiu et al. 2013	6 weekly sessions; 1h	NR	TAU – 6 weekly sessions for mother craft advice and general support
Scott et al. 1997	10 weekly 2h sessions	NR	WL – educational booklet
Serfaty et al 2009	6 weekly sessions; 30m	NR	TAU – ADM, referrals or counseling
Simpson et al. 2003	12 sessions	NR	TAU– GPs; ADM, routine support, referral to other mental services
Smit et al. 2006	6-12; 50min	NR	TAU – routine GP treatment
Swartz et al. 2008	10-12 weekly sessions; 1 hour	NR	TAU - GPs; ADM, routine support, referral to other mental services
Tandon et al. 2014	8 sessions	Naturalistic follow up	TAU – psychoeducation material; referral to community mental health services
Teasdale et al. 1984	6 weekly group sessions; 2h	NR	TAU – home visiting services & information for perinatal depression
Van Schaik et al. 2006	20 sessions; firstly twice weekly and then once a week;1 h	NR	TAU

Continued

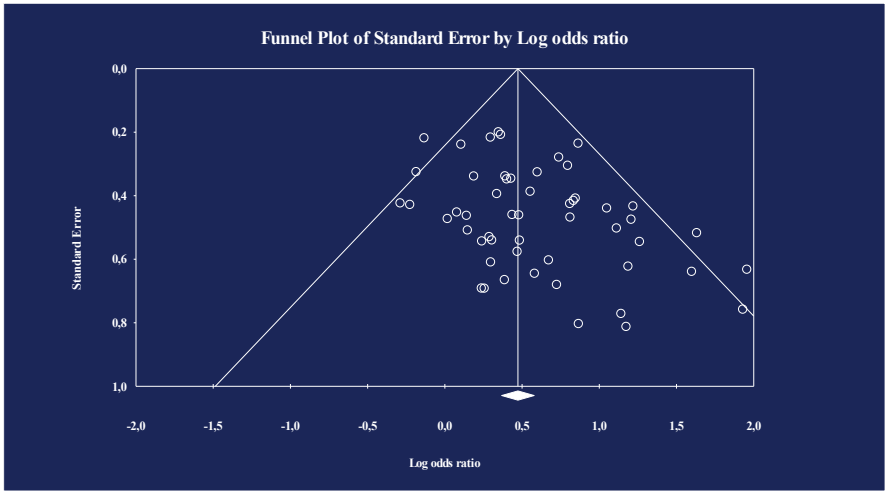
Table a – Additional characteristics of the included RCTs: psychotherapy (acute phase) vs. control groups in adults with depression (Continued)

Studies	N of PT sessions & exact duration	Out-of-protocol interval treatment	Control group – detailed explanation
Verduyn et al. 2003	10 sessions across five months	NR	TAU – GPs (GPs were advised to not prescribe ADM or psychotherapy to patients)
Wiles et al. 2013	16 weekly group sessions; 90 min	NR	No treatment – Routine treatment were available to the patients Placebo PT
Williams et al. 2013	12 sessions; 50-60min	NR	TAU- GPs
Allart-van Dam et al. 2007	3 workbooks per week assisted by 4 f-f sessions	NR	TAU- GPs

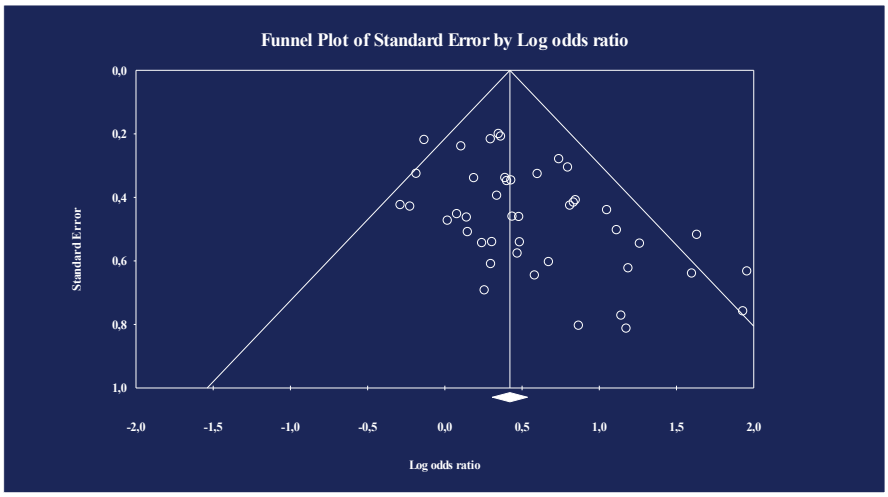
Abbreviations: ADM: Antidepressant Medications; AIDS: Acquired Immune Deficiency Syndrome; CM: Clinical management; FU: Follow Up; GPs: General Practitioners; h: hour(s); HIV: Human Immunodeficiency Virus; LI: Lifestyle Intervention; min: minutes; n: number; NR: Not Reported; NS: Not Specified; PT: Placebo Psychotherapy; TAU: Treatment As Usual; WL: Waiting List

B2. FIGURES

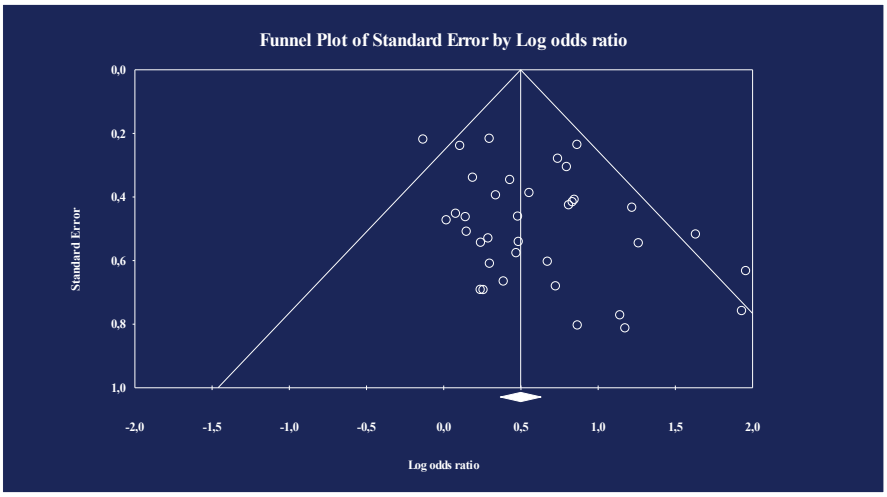
Funnel plots of publication bias, long-term effects of psychotherapy in adults with depression compared to control groups (at ≥ 6 months post-randomization



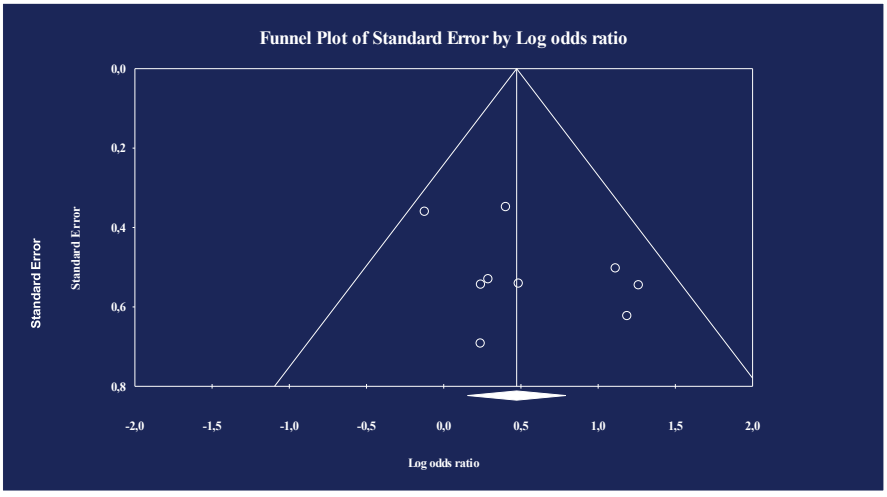
Funnel plot a. All positive outcomes combined (two outliers excluded)



Funnel plot b. All positive outcomes combined (psychotherapy with booster sessions excluded)



Funnel plot c. CBT vs. controls



Funnel plot d. Partial remission

B3. SUPPLEMENTAL MATERIAL

Definitions of different types of psychotherapy

The following text is reproduced from: Cuijpers, P., van Straten, A., Andersson, G., & van Oppen, P. (2008). Psychotherapy for depression in adults: a meta-analysis of comparative outcome studies. *Journal of Consulting and Clinical* Psychology, *76* (6), 909

Page 991, table 1:

1. *Cognitive–behavior therapy (CBT):* In CBT, therapists focus on the impact a patient's present dysfunctional thoughts have on current behavior and future functioning. CBT is aimed at evaluating, challenging, and modifying a patient's dysfunctional beliefs (cognitive restructuring). In this form of treatment, the therapist mostly emphasizes homework assignments and outside-of-session activities. Therapists exert an active influence over therapeutic interactions and topics of discussion, use a psychoeducational approach, and teach patients new ways of coping with stressful situations. We distinguished two main types of CBT: (a) CBT in which cognitive restructuring is the core element of the treatment and (b) CBT in which cognitive restructuring is an important component, but in which at least two other components (such as behavioral activation, social skills training, relaxation, or coping skills) also have a prominent place. One example of this approach is the Coping with Depression course (Lewinsohn et al., 1984). Within the first subtype, we distinguished two variants. Variant a1: The manual developed by Beck et al. (1979) is the most widely used manual for CBT (which includes a module on behavioral activation; see below). Variant a2: In several studies, cognitive restructuring is used as a treatment (with or without a module on behavioral activation), but no explicit reference is made to Beck et al.'s manual.

2. *Nondirective supportive therapy (SUP)*: We defined nondirective therapy as any unstructured therapy without specific psychological techniques other than those common to all approaches, such as helping people to ventilate their experiences and emotions and offering empathy. It is not aimed at solutions or acquiring new skills. It is based on the assumption that relief from personal problems may be achieved through discussion with others. These nondirective therapies are commonly described in the literature as either counseling or supportive therapy. We distinguished two main types of SUP: (a) SUP explicitly referring to the work of Rogers (1967); this is a specific form of nondirective therapy in which reflection is an important therapeutic technique to elicit feelings, and (b) this subtype included the SUP interventions that were not explicitly referring to the work of Rogers, but met the definition of SUP.

3. *Behavioral activation therapy (BA)*: We considered an intervention to be activity scheduling when the registration of pleasant activities and the increase of positive interactions between a person and his or her environment were the core elements of the treatment. Social skills training could be a part of the intervention. Although this intervention was developed by

Lewinsohn et al. (1976), we also included studies that used the principles of this intervention but did not refer directly to the work of Lewinsohn et al. Some studies referred to the behavioral activation component included in the manual for CBT by Beck et al. (1979). This component of CBT is based on similar principles.

4. *Psychodynamic therapy (DYN)*: The primary objective in (short-term) psychodynamic therapy is to enhance the patient's understanding, awareness, and insight about repetitive conflicts (intrapsychic and intrapersonal). An assumption in DYN is that a patient's childhood experiences, past unresolved conflicts, and historical relationships significantly affect a person's present life situation. In this form of treatment, the therapist concentrates on the patient's past, unresolved conflicts, and historical relationships and the impact these have on a patient's present functioning. Furthermore, in DYN the therapists explore a patient's wishes, dreams, and fantasies. The time limitations and the focal explorations of the patient's life and emotions distinguish DYN from psychoanalytic psychotherapy.

5. *Problem-solving therapy (PST)*: We defined PST as a psychological intervention in which the following elements had to be included: definition of personal problems, generation of multiple solutions to each problem, selection of the best solution, the working out of a systematic plan for this solution, and evaluation as to whether the solution has resolved the problem. There are several subtypes of PST, such as PST according to Nezu (1986) and Mynors-Wallis et al. (1995), but the number of studies for each of these subtypes was too small to include in this meta-analysis.

6. *Interpersonal psychotherapy (IPT)*: IPT is a brief and highly structured manual-based psychotherapy that addresses interpersonal issues in depression to the exclusion of all other foci of clinical attention (http://www.interpersonalpsychotherapy.org). IPT has no specific theoretical origin, although its theoretical basis can be seen as coming from the work of Sullivan, Meyer, and Bowlby. The current form of the treatment was developed by the late Gerald Klerman and Myrna Weissman in the 1980s (Klerman et al., 1984).

7. *Social skills training (SST)*: SST is a form of behavior therapy in which clients are taught skills that help in the building and retainment of social and interpersonal relationships. In most versions of SST, patients are trained in assertiveness. This means that the client is taught to stand up for his or her rights by expressing feelings in an honest and respectful way that does not insult people.

APPENDIX C (CHAPTER 3)

C1. FIGURES

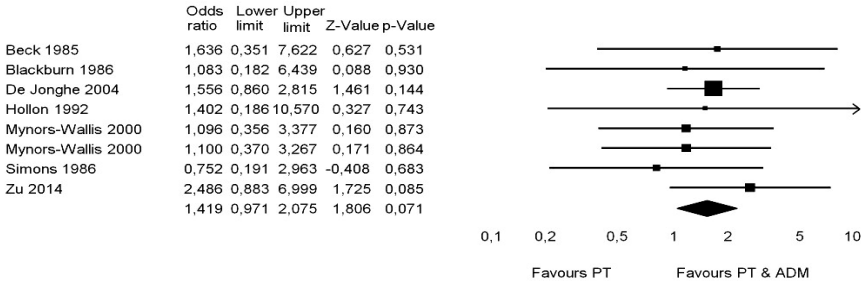


Figure a. Response to acute phase combined PT&ADM vs. PT at 6 months or longer post randomization in patients with MDD

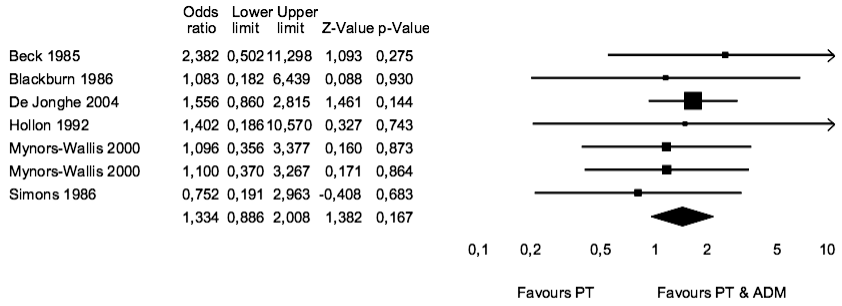


Figure b. Response to acute phase combined PT&ADM vs. PT at 12 months or longer post randomization in patients with MDD

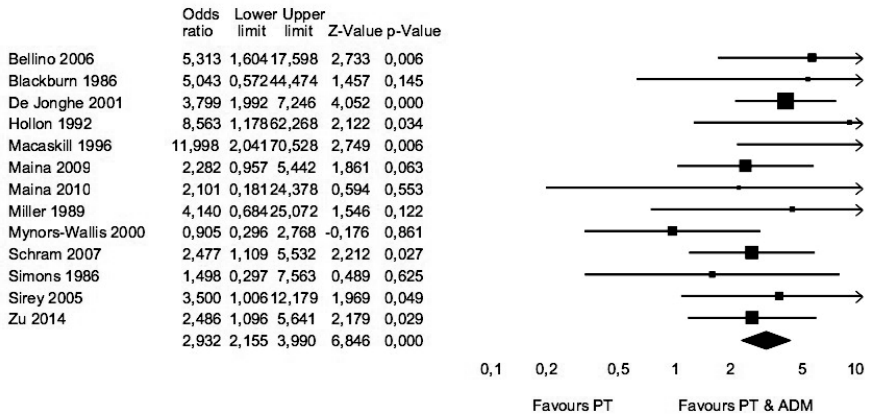


Figure c. Response to acute phase combined PT&ADM vs. ADM at 6 months or longer post randomization in patients with MDD

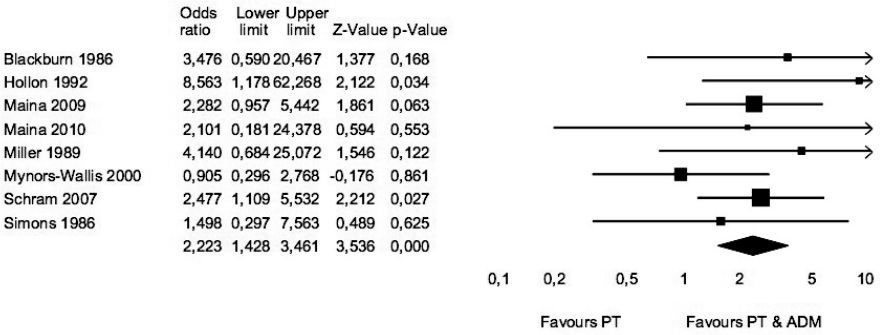


Figure d. Response to acute phase combined PT&ADM vs. ADM at 12 months or longer post randomization in patients with MDD

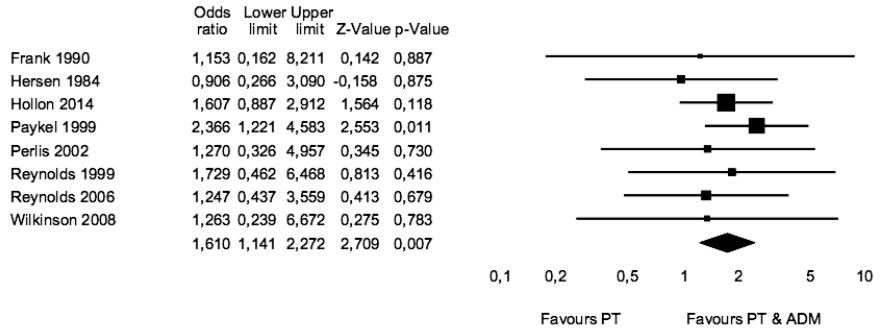


Figure e. Response to combined PT&ADM vs. PT at 6 months or longer post randomization in patients, who had had MDD (maintenance phase)

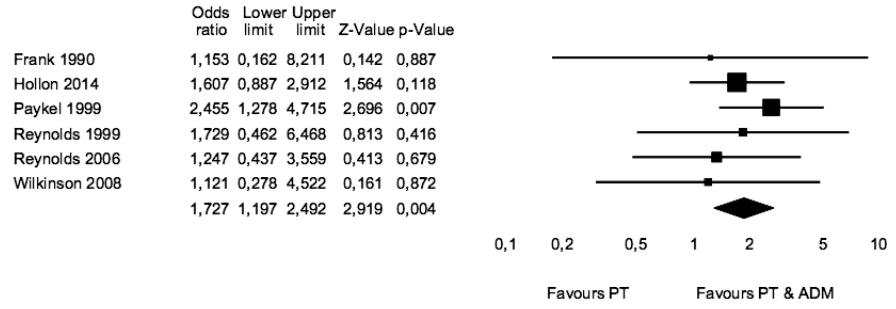


Figure f. Response to combined PT&ADM vs. PT at 12 months or longer post randomization in patients, who had had MDD (maintenance phase)

APPENDIX D (CHAPTER 4)

D1. TABLES

Table a. Reference list of randomized trials comparing psychotherapies for adult depression to control groups in Western countries

Study	Target Group	Diag	Type	Format	Nsess	Control	Region	RoBa)
Allart-Van Dam, Hosman, Hoogduin, & Schaap, 2003	Adults	cutoff	CBT	Grp	12	CAU	EU	– – SR –
Ammerman et al., 2013	Women with PPD	Diag	CBT	Ind	15	CAU	USA	– + + +
Andersson et al., 2005	Adults	cutoff	CBT	Gsh	5	Other	EU	+ + SR +
Arean et al., 1993	Elderly	Diag	PST	Grp	12	WL	USA	– – + –
Arean, 1993 rem	Elderly	Diag	Other	Grp	12	WL	USA	– – + –
Ayen & Hautzinger, 2004	Adults	Diag	CBT	Grp	12	WL	EU	– – SR +
Ayen, 2004 sup	Adults	Diag	SUP	Grp	12	WL	EU	– – SR +
Barber, Barrett, Gallop, Rynn, & Rickels, 2012	Adults	Diag	DYN	Ind	20	Other	USA	+ – + +
Barlow, 1896	Elderly	cutoff	Other	Grp	6	WL	USA	– – SR –
Barnhofer et al., 2009	Adults	Diag	MBCT	Grp	8	CAU	EU	+ + SR +
Barrera, 1979	Adults	cutoff	BAT	Grp	8	WL	USA	– – SR –
Barrett et al., 2001	Adults	Diag	PST	Ind	6	Other	USA	+ + SR +
Beach & O'Leary, 1992	Other	Diag	CBT	Ind	18	WL	USA	– – SR –
Beach, 1992 mar	Other	Diag	CBT	Other	18	WL	USA	– – SR –
Bedard et al., 2014	General Med. Dis.	cutoff	MBCT	Grp	10	WL	USA	+ + SR –
Beeber et al., 2010	Other	cutoff	IPT	Ind	16	CAU	USA	– – SR –
Berger, Hammerli, Gubser, Andersson, & Caspar, 2011	Adults	Diag	CBT	Gsh	10	WL	EU	+ + SR +

continued

Table a. Reference list of randomized trials comparing psychotherapies for adult depression to control groups in Western countries (continued)

Study	Target Group	Diag	Type	Format	Nsess	Control	Region	RoBa)
Beutel et al., 2014	General Med. Dis.	Diag	DYN	Ind	20	CAU	EU	+ + + +
Bohlmeijer, Fledderus, Rokx, & Pieterse, 2011	Adults	cutoff	Other	Grp	8	WL	EU	+ + SR +
Bolton et al., 2003	Adults	Diag	IPT	Grp	16	CAU	Africa	+ – SR +
Bowman, Scogin, & Lyrene, 1995	Adults	cutoff	CBT	Gsh	4	WL	USA	– – – –
Bowman, 1995 se	Adults	cutoff	PST	Gsh	4	WL	USA	– – – –
Brown & Lewinsohn, 1984	Adults	Diag	CBT	Grp	12	WL	USA	– – SR –
Brown, 1984 gsh	Adults	Diag	CBT	Gsh	12	WL	USA	– – SR –
Brown, 1984 ind	Adults	Diag	CBT	Ind (tel)	12	WL	USA	– – SR –
Buhrman et al., 2015	General Med. Dis.	cutoff	CBT	Gsh	8	Other	EU	+ + SR +
Buntrock et al., 2015	Adults	cutoff	CBT	Gsh	6	CAU	EU	+ + + +
Alistair Burns et al., 2007	Elderly	cutoff	Other	Ind	6	CAU	EU	+ + + +
Burns et al., 2013	Women with PPD	cutoff	CBT	Ind	12	CAU	EU	+ + SR +
Carlbring et al., 2013	Adults	Diag	Other	Gsh	7	WL	EU	+ + SR +
Carrington, 1979	Other	Diag	CBT	Ind	12	WL	USA	– – SR –
Carrington, 1979 dyn	Other	Diag	DYN	Ind	12	WL	USA	– – SR –
Casanas et al., 2012	Adults	Diag	CBT	Grp	12	CAU	EU	+ + SR +
Castonguay et al., 2004	Adults	Diag	CBT	Ind	16	WL	USA	– – + –
Chan et al., 2012) - CBT	Adults	Diag	CBT	Ind	10	WL	Asia	– + + –
Chan, 2012 – MBCT	Adults	Diag	Other	Ind	10	WL	Asia	– + + –
Chan, Ng, Tien, Man Ho, & Thayala, 2013	Older Adults	Cutoff	Other	Ind	5	CAU	Asia	+ – SR +
Chen, Tseng, Chou, & Wang, 2000	Women with PPD	Cutoff	SUP	Grp	4	CAU	Asia	– – SR –
Chesney, Chambers, Taylor, Johnson, & Folkman, 2003	General Med. Dis.	cutoff	Other	Grp	10	WL	USA	– – SR –

continued

Table a. Reference list of randomized trials comparing psychotherapies for adult depression to control groups in Western countries (continued)

Study	Target Group	Diag	Type	Format	Nsess	Control	Region	RoBa)
Chiang et al., 2015	Adults	Diag	CBT	Grp	12	CAU	Asia	+ + + –
Cho, Kwon, & Lee, 2008	Women with PPD	Diag	CBT	Ind	9	CAU	Asia	– – SR –
Choi, 2012(I. Choi et al., 2012)	Other	Diag	CBT	Gsh	6	WL	AUS	+ + SR –
Choi, 2013 ftf(N. G. Choi, Marti, Bruce, & Hegel, 2013)	Elderly	cutoff	PST	Ind	6	WL	USA	– – – +
Choi, 2013 tel	Elderly	cutoff	PST	Ind (tel)	6	WL	USA	– – – +
Chronis, 2013(Chronis-Tuscano et al., 2013)	Other	cutoff	CBT	Grp	14	Other	USA	– – SR +
Clark, 2003 ipt(Clark, Tluczek, & Wenzel, 2003)	Women with PPD	Diag	IPT	Ind	12	WL	USA	– – SR –
Clark, 2003 m-itg	Women with PPD	Diag	Other	Grp	12	WL	USA	– – SR –
Clark, 2008(Clark, Tluczek, & Brown, 2008)	Women with PPD	Diag	Other	Grp	12	WL	USA	– – SR –
Cohen, 2010(Cohen, O'Leary, & Foran, 2010)	Adults	Diag	Other	Ind	5	WL	USA	– – + –
Cooper, Murray, Wilson, & Romaniuk, 2003	Women with PPD	Diag	CBT	Ind	10	CAU	EU	+ + SR –
Cooper, 2003 dyn	Women with PPD	Diag	DYN	Ind	10	CAU	EU	+ + SR –
Cooper, 2003 sup	Women with PPD	Diag	SUP	Ind	10	CAU	EU	+ + SR –
Cramer, Salisbury, Conrad, Eldred, & Araya, 2011	Other	cutoff	CBT	Grp	12	CAU	EU	+ – SR +
Cullen, 2002	Adults	Diag	BAT	Ind	10	WL	USA	– – SR –
Dekker, Moser, Peden, & Lennie, 2012	General Med. Dis.	cutoff	CBT	Ind	2	CAU	USA	+ + SR +
DeRubeis et al., 2005	Adults	Diag	CBT	Ind	20	Other	USA	– – + +
Dimidjian et al., 2006	Adults	Diag	CBT	Ind	24	Other	USA	+ – + +
Dimidjian, 2006 ct	Adults	Diag	BAT	Ind	24	Other	USA	+ – + +
Dindo, Recober, Marchman, Turvey, & O'Hara, 2012	General Med. Dis.	Diag	Other	Grp	1	WL	USA	– – – +
Dobkin et al., 2011	General Med. Dis.	Diag	CBT	Ind	10	CAU	USA	+ – + +
Doering et al., 2013	General Med. Dis.	Diag	CBT	Ind	8	CAU	USA	+ – SR +

continued

Table a. Reference list of randomized trials comparing psychotherapies for adult depression to control groups in Western countries (continued)

Study	Target Group	Diag	Type	Format	Nsess	Control	Region	RoBa)
Dowrick et al., 2000	Adults	Diag	CBT	Grp	12	CAU	EU	+ + SR +
Dowrick, 2000 pst	Adults	Diag	PST	Ind	6	CAU	EU	+ + SR +
Duarte, Miyazaki, Blay, & Sesso, 2009	General Med. Dis.	Diag	CBT	Grp	12	CAU	L-Am	– + SR –
Duchac, 2002	Other	Diag	CBT	Grp	6	CAU	USA	+ – – +
Dwight-Johnson et al., 2011	Other	cutoff	CBT	Ind	8	CAU	USA	+ – + +
Ekers, Richards, McMillan, Bland, & Gilbody, 2011	Adults	Diag	BAT	Ind	12	CAU	EU	+ + SR +
Elkin et al., 1989	Adults	Diag	CBT	Ind	16	Other	USA	+ – + –
Elkin, 1989 ipt	Adults	Diag	IPT	Ind	16	Other	USA	+ – + –
Epstein, 1986	Adults	Diag	CBT	Grp	8	WL	USA	– – SR –
Evans & Connis, 1995	General Med. Dis.	cutoff	CBT	Grp	8	Other	USA	– – SR –
Evans, 1995 sup	General Med. Dis.	cutoff	SUP	Grp	8	Other	USA	– – SR –
Fann et al., 2015	General Med. Dis.	Diag	CBT	Ind	12	CAU	USA	+ – + –
Fann, 2015 tel	General Med. Dis.	Diag	CBT	Ind (tel)	12	CAU	USA	+ – + –
Faramarzi et al., 2008	Other	Diag	CBT	Grp	10	CAU	Africa	– – SR –
Fledderus, Bohlmeijer, Pieterse, & Schreurs, 2012 act-e	Adults	cutoff	Other	Gsh	9	WL	EU	+ – SR +
Fledderus, 2012 act-m	Adults	cutoff	Other	Gsh	9	WL	EU	+ – SR +
Floyd, Scogin, McKendree-Smith, Floyd, & Rokke, 2004	Elderly	Diag	CBT	Gsh	4	WL	USA	– – – –
Floyd, 2004 ind	Elderly	Diag	CBT	Ind	16	WL	USA	– – – –
Folke, Parling, & Melin, 2012	Other	Diag	Other	Other	6	CAU	EU	– – SR +
Forsyth, 2000	Students	Diag	IPT	Grp	4	WL	USA	– – SR –
Freedland et al., 2009	General Med. Dis.	Diag	CBT	Ind	12	CAU	USA	+ + + +

continued

Table a. Reference list of randomized trials comparing psychotherapies for adult depression to control groups in Western countries (continued)

Study	Target Group	Diag	Type	Format	Nsess	Control	Region	RoBa)
Freedland, 2009 ssm	General Med. Dis.	Diag	SUP	Ind	12	CAU	USA	+ + + +
Freedland, Carney, Rich, Steinmeyer, & Rubin, 2015	General Med. Dis.	Diag	CBT	Ind	24	CAU	USA	+ + + +
Frothingham, 2005	General Med. Dis.	Diag	CBT	Grp	8	Other	USA	– – SR –
Fry, 1983	Elderly	cutoff	Other	Ind	5	Other	USA	– – SR –
Fry, 1983 unstr rem	Elderly	cutoff	Other	Ind	5	Other	USA	– – SR –
Furukawa et al., 2012	Adults	Cutoff	CBT	Ind	8	WL	Asia	+ + SR +
García-Peña et al., 2015	Older Adults	Cutoff	CBT	Grp	12	CAU	L-Am	+ – SR –
Gawrysiak, Nicholas, & Hopko, 2009	Students	cutoff	BAT	Ind	1	CAU	USA	– – SR +
Gehr, 1988	Adults	cutoff	Other	Ind	7	Other	USA	– – SR –
Gellis & Bruce, 2010	Elderly	cutoff	PST	Ind	6	CAU	USA	+ – + –
Geraedts, Kleiboer, Wiezer, van Mechelen, & Cuijpers, 2014	Adults	cutoff	CBT	Gsh	6	CAU	EU	+ + SR +
Gitlin et al., 2013	Elderly	cutoff	Other	Ind	10	WL	USA	+ + SR +
Goodman, Prager, Goldstein, & Freeman, 2015	Women with PPD	cutoff	Other	Ind	8	CAU	USA	– + SR +
Grote et al., 2009	Women with PPD	cutoff	IPT	Ind	8	CAU	USA	– – SR –
Hallgren et al., 2015	Adults	cutoff	CBT	Gsh		CAU	EU	+ + + –
Hamamci, 2006	Students	Cutoff	CBT	Grp	11	CAU	EU	– – SR –
Hamamci, 2006 – CT+DR	Students	Cutoff	CBT	Grp	11	CAU	EU	– – SR –
Hamdan-Mansour, Puskar, & Bandak, 2009	Students	Cutoff	CBT	Grp	10	CAU	Africa	– + SR –
Haringsma, Engels, Cuijpers, & Spinhoven, 2006	Elderly	cutoff	CBT	Grp	10	WL	EU	– – SR +
Harley, Sprich, Safren, Jacobo, & Fava, 2008	Adults	Diag	Other	Grp	16	WL	USA	– – + –
Hassiotis et al., 2013	Other	Diag	CBT	Ind	16	CAU	EU	– + SR +

continued

Table a. Reference list of randomized trials comparing psychotherapies for adult depression to control groups in Western countries (continued)

Study	Target Group	Diag	Type	Format	Nsess	Control	Region	RoBa)
Hautzinger & Welz, 2004	Elderly	Diag	CBT	Grp	12	WL	EU	+ – SR +
Hayman & Cope, 1980	Adults	cutoff	Other	Grp	8	WL	USA	+ – SR –
Heckman et al., 2011	General Med. Dis.	cutoff	Other	Grp	12	Other	USA	+ – SR +
Heckman, 2011 sup	General Med. Dis.	cutoff	Other	Grp	12	Other	USA	+ – SR +
Hegerl et al., 2010	Adults	cutoff	CBT	Grp	10	Other	EU	+ + + +
Hermanns et al., 2015	General Med. Dis.	cutoff	CBT	Grp	5	Other	EU	– + SR +
Hogg & Deffenbacher, 1988	Students	cutoff	CBT	Grp	8	WL	USA	– – SR –
Hogg, 1988 interp	Students	cutoff	Other	Grp	8	WL	USA	– – SR –
Holden, Sagovsky, & Cox, 1989	Women with PPD	Diag	SUP	Ind	8	CAU	EU	+ – + –
Honey, Bennett, & Morgan, 2002	Women with PPD	cutoff	CBT	Grp	8	CAU	EU	– – SR +
Horrell et al., 2014	Adults	cutoff	CBT	Grp	4	WL	EU	+ + SR +
Hou et al., 2014	Women with PPD	Diag	CBT	Other	19	CAU	Asia	– – SR –
Huang et al., 2015	General Med. Dis.	Cutoff	CBT	Grp	12	CAU	Asia	– – SR –
Hunter, Witkiewitz, Watkins, Paddock, & Hepner, 2012	Other	cutoff	CBT	Grp	18	CAU	USA	– – SR +
Jamison & Scogin, 1995	Adults	Diag	CBT	Gsh	4	WL	USA	– – – –
Jarrett et al., 1999	Adults	Diag	CBT	Ind	20	Other	USA	– + + +
Jesse et al., 2015	Women with PPD	cutoff	CBT	Grp	6	CAU	USA	+ + SR –
Jiang et al., 2014	Women with PPD	Cutoff	Other	Ind		CAU	Asia	+ – SR –
Johansson, Ekbladh, et al., 2012	Adults	Diag	DYN	Gsh	9	Other	EU	+ + SR +
Johansson, Sjˆberg, et al., 2012	Adults	Diag	CBT	Gsh	8	Other	EU	+ + SR –
Johansson, 2012b tayl	Adults	Diag	CBT	Gsh	10	Other	EU	+ + SR –

continued

Table a. Reference list of randomized trials comparing psychotherapies for adult depression to control groups in Western countries (continued)

Study	Target Group	Diag	Type	Format	Nsess	Control	Region	RoBa)
Johnson & Zlotnick, 2012	Other	Diag	IPT	Other	33	Other	USA	– + + +
Joling et al., 2011	Elderly	cutoff	CBT	Gsh	36	CAU	EU	+ + SR +
Kanter et al., 2015	Other	Diag	BAT	Ind	12	CAU	USA	+ – + +
Kelly et al., 1993 cbt	General Med. Dis.	cutoff	CBT	Grp	8	CAU	USA	– – SR –
Kelly, 1993 sup	General Med. Dis.	cutoff	SUP	Grp	8	CAU	USA	– – SR –
Kessler et al., 2009	Adults	Diag	CBT	Gsh	10	WL	EU	+ + SR +
King et al., 2000	Adults	cutoff	CBT	Ind	6	CAU	EU	– + SR +
King, 2000 sup	Adults	cutoff	SUP	Ind	6	CAU	EU	– + SR +
Kivi et al., 2014	Adults	Diag	CBT	Gsh	7	CAU	EU	– + SR –
Kleiboer et al., 2015	Adults	cutoff	PST	Gsh	5	WL	EU	+ + SR +
Korrelboom, Maarsingh, & Huijbrechts, 2012	Adults	Diag	Other	Grp	8	CAU	EU	– + SR +
Korte, Bohlmeijer, Cappeliez, Smit, & Westerhof, 2012	Elderly	cutoff	Other	Grp	8	CAU	EU	+ + SR +
Krampen, 1997	Adults	Diag	Other	Ind	20	WL	EU	– – SR –
Krampen, 1997 ind	Adults	Diag	CBT	Ind	20	WL	EU	– – SR –
Laidlaw et al., 2008	Elderly	Diag	CBT	Ind	8	CAU	EU	+ + + –
Lamers et al., 2010	Elderly	Diag	CBT	Ind	6	CAU	EU	+ + SR +
Lamers, Bohlmeijer, Korte, & Westerhof, 2015	Adults	cutoff	Other	Ind	7	CAU	EU	+ + SR +
Landreville & Bissonnette, 1997	Elderly	cutoff	CBT	Gsh	4	WL	USA	– – SR –
Lappalainen, Langrial, Oinas-Kukkonen, Tolvanen, & Lappalainen, 2015	Adults	Diag	Other	Gsh	6	WL	EU	– + SR +
Larcombe & Wilson, 1984	General Med. Dis.	Diag	CBT	Grp	6	WL	AUS	– – + –
Lemma & Fonagy, 2013	Adults	cutoff	DYN	Grp	8	Other	EU	– – SR –

continued

Table a. Reference list of randomized trials comparing psychotherapies for adult depression to control groups in Western countries (continued)

Study	Target Group	Diag	Type	Format	Nsess	Control	Region	RoBa)
Leung et al., 2013	Women with PPD	Cutoff	CBT	Grp	6	CAU	Asia	– – SR +
Lexis et al., 2011	Adults	cutoff	PST	Ind	10	CAU	EU	+ – SR +
Linde et al., 2011	Other	Diag	CBT	Grp	26	Other	USA	+ + SR +
Liu et al., 2009	Adults	Cutoff	CBT	Gsh	10	WL	Asia	– – SR –
Losada et al., 2015 act	Other	cutoff	Other	Ind	8	Other	EU	+ – SR –
Losada, 2015 cbt	Other	cutoff	CBT	Ind	8	Other	EU	+ – SR –
Lovell et al., 2008	Adults	cutoff	CBT	Gsh	7	CAU	EU	– + SR +
Lustman, Griffith, Freedland, Kissel, & Clouse, 1998	General Med. Dis.	Diag	CBT	Ind	10	CAU	USA	+ + SR –
Lynch, Tamburrino, & Nagel, 1997	Adults	cutoff	PST	Ind (tel)	6	CAU	USA	– – SR –
Lynch, Tamburrino, Nagel, & Smith, 2004	Adults	cutoff	PST	Ind (tel)	6	CAU	USA	– – + –
MacPherson et al., 2013	Adults	cutoff	SUP	Ind	12	CAU	EU	+ + SR +
Maina, Forner, & Bogetto, 2005 bdt	Adults	Diag	DYN	Ind	20	WL	EU	– – + +
Maina, 2005 bsp	Adults	Diag	SUP	Ind	20	WL	EU	– – + +
Malouff, Lanyon, & Schutte, 1988	Other	cutoff	PST	Grp	4	WL	USA	– – SR –
Malouff, 1988 ret	Other	cutoff	CBT	Grp	4	WL	USA	– – SR –
Martin et al., 2015	General Med. Dis.	Diag	CBT	Ind	12	CAU	AUS	+ + SR –
McClay et al., 2015	Adults	cutoff	CBT	Grp gsh	8	CAU	EU	– + SR –
McKee, Zayas, Fletcher, Boyd, & Nam, 2006	Women with PPD	cutoff	CBT	Ind	5	CAU	USA	– – SR –
McKendree, 1998 beh(McKendree-Smith, 1998)	Adults	Diag	CBT	Gsh	8	WL	USA	– – + –
McKendree, 1998 cogn	Adults	Diag	CBT	Gsh	8	WL	USA	– – + –
Michalak, Schultze, Heidenreich, & Schramm, 2015	Adults	Diag	Other	Grp	10	CAU	EU	+ + + +
Michalak, 2015 mbct	Adults	Diag	MBCT	Grp	8	CAU	EU	+ + + +

continued

Table a. Reference list of randomized trials comparing psychotherapies for adult depression to control groups in Western countries (continued)

Study	Target Group	Diag	Type	Format	Nsess	Control	Region	RoBa)
Milgrom, Negri, Gemmill, McNeil, & Martin, 2005	Women with PPD	Diag	CBT	Grp	9	CAU	AUS	+ + SR +
Milgrom, 2005 grp sup	Women with PPD	Diag	SUP	Grp	9	CAU	AUS	+ + SR +
Milgrom, 2005 ind sup	Women with PPD	Diag	SUP	Ind	9	CAU	AUS	+ + SR +
Milgrom et al., 2011	Women with PPD	cutoff	CBT	Ind	6	CAU	AUS	+ + SR +
Milgrom, 2011 psy	Women with PPD	cutoff	CBT	Ind	6	CAU	AUS	+ + SR +
Milgrom et al., 2015	Women with PPD	Diag	CBT	Ind	8	CAU	AUS	+ + SR +
Miller & Weissman, 2002	Adults	cutoff	IPT	Ind (tel)	12	CAU	USA	– – + –
Miranda et al., 2003	Other	Diag	CBT	Other	8	CAU	USA	+ + + +
Mohr et al., 2000	General Med. Dis.	cutoff	CBT	Ind (tel)	8	CAU	USA	– – SR +
Mohr, Carmody, Erickson, Jin, & Leader, 2011	Adults	Diag	CBT	Ind (tel)	16	CAU	USA	– – + +
David C Mohr et al., 2013)	Adults	Diag	CBT	Gsh	18	WL	USA	+ + SR +
Moldovan, Cobeanu, & David, 2013	Students	cutoff	CBT	Gsh	4	WL	EU	+ + SR +
Morris, 1975	Other	cutoff	CBT	Grp	6	WL	USA	– – SR –
Mossey, Knott, Higgins, & Talerico, 1996	Elderly	cutoff	IPT	Ind	10	CAU	USA	– – SR –
Mukhtar, 2011	Adults	Diag	CBT	Grp	8	WL	Asia	– – SR –
Mulcahy, Reay, Wilkinson, & Owen, 2010	Women with PPD	Diag	IPT	Grp	11	CAU	AUS	+ – – –
Mynors-Wallis, Gath, Lloyd-Thomas, & Tomlinson, 1995	Adults	Diag	PST	Ind	6	Other	EU	– + + –
Naeem et al., 2014	Adults	Cutoff	CBT	Gsh	7	CAU	Asia	+ – SR –
Nakimuli-Mpungu et al., 2015	General Med. Dis.	Diag	Other	Grp	8	Other	Africa	+ + SR +
Neugebauer et al., 2006	Other	cutoff	IPT	Ind	6	CAU	USA	– – + +

continued

Table a. Reference list of randomized trials comparing psychotherapies for adult depression to control groups in Western countries (continued)

Study	Target Group	Diag	Type	Format	Nsess	Control	Region	RoBa)
Nezu, 1986 pf	Adults	Diag	PST	Grp	8	WL	USA	– – SR –
Nezu, 1986 pst	Adults	Diag	PST	Grp	8	WL	USA	– – SR –
Nezu & Perri, 1989 apst	Adults	Diag	PST	Grp	10	WL	USA	– – + –
Nezu, 1989 pst	Adults	Diag	PST	Grp	10	WL	USA	– – + –
Ng, Tien, Thayala, Ho, & Chan, 2013	Older Adults	Cutoff	Other	Ind	5	CAU	Asia	– – SR –
Ngai, Wong, Leung, Chau, & Chung, 2015	Women with PPD	Cutoff	CBT	Other	5	CAU	Asia	+ + SR +
Nobis et al., 2015	General Med. Dis.	cutoff	Other	Gsh	6	Other	EU	+ – SR +
O'Hara, Stuart, Gorman, & Wenzel, 2000	Women with PPD	Diag	IPT	Ind	12	WL	USA	+ – – +
O'Mahen, Himle, Fedock, Henshaw, & Flynn, 2013a	Women with PPD	Diag	CBT	Ind	12	CAU	USA	+ + SR +
O'Mahen et al., 2013	Women with PPD	cutoff	BAT	Gsh	11	CAU	EU	+ + SR –
O'Neil et al., 2014	General Med. Dis.	cutoff	CBT	Ind (tel)	10	CAU	AUS	+ + + +
Omidi, Mohammadkhani, Mohammadi, & Zargar, 2013	Adults	Diag	CBT	Grp	8	CAU	Africa	– – SR –
Omidi, 2013 – MBCT	Adults	Diag	CBT	Grp	8	CAU	Africa	– – SR –
Pace & Dixon, 1993	Students	cutoff	CBT	Ind	7	WL	USA	– – SR –
Pagoto et al., 2013	Other	Diag	BAT	Other	26	Other	USA	+ + SR +
Pecheur & Edwards, 1984	Students	Diag	CBT	Ind	8	WL	USA	– – + –
Pecheur, 1984 scbm	Students	Diag	CBT	Ind	8	WL	USA	– – + –
Peden, Hall, Rayens, & Beebe, 2000	Students	cutoff	CBT	Grp	6	CAU	USA	– – SR –
Penckofer et al., 2012	General Med. Dis.	cutoff	CBT	Grp	8	CAU	USA	+ – SR +
Perini, Titov, & Andrews, 2009	Adults	Diag	CBT	Gsh	6	WL	AUS	+ – SR –
Petersen, Hanass Hancock, Bhana, & Govender, 2014	General Med. Dis.	Diag	IPT	Grp	8	CAU	Africa	+ – SR –
Pibernik-Okanovic, Begic, Ajdukovic, Andrijasevic, & Metelko, 2009	General Med. Dis.	cutoff	CBT	Grp	4	CAU	EU	– + SR –

continued

Table a. Reference list of randomized trials comparing psychotherapies for adult depression to control groups in Western countries (continued)

Study	Target Group	Diag	Type	Format	Nsess	Control	Region	RoBa)
Poleshuck et al., 2014	General Med. Dis.	Diag	IPT	Ind	8	CAU	USA	+ – – +
Pot et al., 2010	Elderly	cutoff	Other	Grp	12	Other	EU	– + SR +
Pots, Meulenbeek, Veehof, Klungers, & Bohlmeijer, 2014	Adults	cutoff	MBCT	Grp	11	WL	EU	+ + SR +
Power Michael & Freeman, 2012 cbt	Adults	Diag	CBT	Ind	16	CAU	EU	– – SR +
Power, 2012 ipt	Adults	Diag	IPT	Ind	16	CAU	EU	– – SR +
Prendergast & Austin, 2001	Women with PPD	Diag	CBT	Ind	6	Other	AUS	+ – – –
Preschl et al., 2012	Elderly	cutoff	Other	Ind	8	WL	EU	+ – SR +
Propst, Ostrom, Watkins, Dean, & Mashburn, 1992 nrct-nt	Adults	cutoff	CBT	Ind	18	Other	USA	– – + –
Propst, 1992 nrct-rt	Adults	cutoff	CBT	Ind	18	Other	USA	– – + –
Propst, 1992 rct-nt	Adults	cutoff	CBT	Ind	18	Other	USA	– – + –
Propst, 1992 rct-rt	Adults	cutoff	CBT	Ind	18	Other	USA	– – + –
Puckering, McIntosh, Hickey, & Longford, 2010	Women with PPD	cutoff	Other	Grp	14	WL	EU	+ – SR –
Pugh, 2014	Women with PPD	cutoff	CBT	Gsh	12	WL	USA	+ + SR –
Qiu et al., 2013	General Med. Dis.	Diag	CBT	Grp	10	WL	Asia	+ + + +
Rahman, Malik, Sikander, Roberts, & Creed, 2008	Women with PPD	Diag	CBT	Ind	16	Other	Asia	+ + + –
Ransom et al., 2008	General Med. Dis.	Diag	IPT	Ind	6	CAU	USA	– – SR +
Rehm et al., 1981 sc	Adults	cutoff	Other	Grp	7	WL	USA	– – SR –
Rehm, 1981 sm	Adults	cutoff	Other	Grp	7	WL	USA	– – SR –
Rehm, 1981 sm+se	Adults	cutoff	Other	Grp	7	WL	USA	– – SR –
Rehm, 1981 sm+sr	Adults	cutoff	Other	Grp	7	WL	USA	– – SR –
Richards et al., 2015	Adults	cutoff	CBT	Gsh	7	WL	EU	– + SR +
Rizvi, Zaretsky, Schaffer, & Levitt, 2015	Adults	Diag	CBT	Ind	14	WL	USA	– – – –

continued

Table a. Reference list of randomized trials comparing psychotherapies for adult depression to control groups in Western countries (continued)

Study	Target Group	Diag	Type	Format	Nsess	Control	Region	RoBa)
Rohan et al., 2007	Adults	Diag	CBT	Grp	12	WL	USA	+ – + +
Rohen, 2002	Adults	cutoff	CBT	Gsh	4	WL	USA	– – + +
Rohricht, Papadopoulos, & Priebe, 2013	Adults	Diag	Other	Grp	20	Other	EU	+ + + +
Ross & Scott, 1985	Adults	Diag	CBT	Other	12	WL	EU	– – SR –
Rude, 1986	Other	cutoff	Other	Grp	12	WL	USA	– – SR –
Ruwaard et al., 2009	Adults	cutoff	CBT	Gsh	8	WL	EU	+ – SR +
Safren et al., 2009	General Med. Dis.	Diag	CBT	Ind	11	CAU	USA	– – + +
Safren et al., 2014)	General Med. Dis.	Diag	CBT	Ind	11	CAU	USA	+ + + –
Savard et al., 2006	General Med. Dis.	cutoff	CBT	Ind	8	WL	USA	+ + + –
Schmidt & Miller, 1983	Adults	cutoff	CBT	Other	8	WL	USA	– – SR –
Schmidt, 1983 ind	Adults	cutoff	CBT	Ind	8	WL	USA	– – SR –
Schmidt, 1983 lgrp	Adults	cutoff	CBT	Grp	8	WL	USA	– – SR –
Schmidt, 1983 sgrp	Adults	cutoff	CBT	Grp	8	WL	USA	– – SR –
Schmitt, 1988	Adults	Diag	PST	Grp	12	WL	USA	– – – –
Schmitt, 1988 sst	Adults	Diag	Other	Grp	12	WL	USA	– – – –
Schulberg et al., 1996	Adults	Diag	IPT	Ind	16	CAU	USA	– – + +
Forrest Scogin, Hamblin, & Beutler, 1987	Elderly	cutoff	CBT	Gsh	4	Other	USA	– – – –
Scogin, Jamison, & Gochneaur, 1989 beh	Elderly	cutoff	CBT	Gsh	4	WL	USA	– – – –
Scogin, 1989 cogn	Elderly	cutoff	CBT	Gsh	4	WL	USA	– – – –
Scogin, Moss, Harris, & Presnell, 2014	Elderly	cutoff	CBT	Ind	16	Other	USA	+ + SR +
Scott & Stradling, 1990 cbt	Adults	Diag	CBT	Grp	12	WL	EU	– – SR +
Scott, 1990 ict	Adults	Diag	CBT	Ind	12	WL	EU	– – SR +

continued

Table a. Reference list of randomized trials comparing psychotherapies for adult depression to control groups in Western countries (continued)

Study	Target Group	Diag	Type	Format	Nsess	Control	Region	RoBa)
Scott & Freeman, 1992)	Adults	Diag	CBT	Ind	16	CAU	EU	– + + –
Scott, 1992 sup	Adults	Diag	SUP	Ind	16	CAU	EU	– + + –
Scott, Tacchi, Jones, & Scott, 1997	Adults	Diag	CBT	Ind	6	CAU	EU	– – + –
Segre, Brock, & O'Hara, 2015	Other	cutoff	Other	Ind	6	WL	USA	+ – + +
Selmi, Klein, Greist, Sorrell, & Erdman, 1990 ccbt	Adults	Diag	CBT	Other	6	WL	USA	– – + +
Selmi, 1990 icbt	Adults	Diag	CBT	Ind	6	WL	USA	– – + +
Serfaty et al., 2009	Elderly	Diag	CBT	Ind	12	CAU	EU	+ + SR +
Serrano, Latorre, Gatz, & Montanes, 2004	Elderly	cutoff	Other	Ind	4	CAU	EU	– – SR –
Serrano Selva et al., 2012	Elderly	Diag	Other	Ind	4	CAU	EU	– – + +
Shaw, 1977	Students	cutoff	BAT	Grp	4	WL	USA	– – SR –
Shaw, 1977 cbt	Students	cutoff	CBT	Grp	4	WL	USA	– – SR –
Shaw, 1977 sup	Students	cutoff	SUP	Grp	4	WL	USA	– – SR –
Sheeber et al., 2012	Women with PPD	cutoff	CBT	Gsh	8	WL	USA	+ + SR +
Simpson, Corney, Fitzgerald, & Beecham, 2000	Adults	cutoff	DYN	Ind	5	CAU	EU	+ + SR +
Simson et al., 2008	General Med. Dis.	cutoff	SUP	Ind	5	CAU	EU	– – SR +
Skinner, 1983 bat	Adults	cutoff	BAT	Ind	5	Other	USA	– – SR –
Skinner, 1983 cbt	Adults	cutoff	CBT	Ind	5	Other	USA	– – SR –
Sloane, Staples, & Schneider, 1985	Elderly	Diag	IPT	Ind	16	Other	USA	– – – –
Smit et al., 2006	Adults	Diag	CBT	Ind	15	CAU	EU	+ + SR –
Songprakun & McCann, 2012	Adults	Diag	CBT	Gsh	8	CAU	Asia	+ + + –
Spek et al., 2007	Elderly	cutoff	CBT	Grp	10	WL	EU	+ + SR +
Spinelli & Endicott, 2003	Other	Diag	IPT	Ind	16	Other	USA	– – – +

continued

Table a. Reference list of randomized trials comparing psychotherapies for adult depression to control groups in Western countries (continued)

Study	Target Group	Diag	Type	Format	Nsess	Control	Region	RoBa)
Spinelli et al., 2013	Women with PPD	Diag	IPT	Ind	12	Other	USA	+ – – –
Sreevani et al., 2013	Adults	Diag	Other	Grp	4	CAU	Asia	+ – SR –
Strauss, Hayward, & Chadwick, 2012	Adults	Diag	MBCT	Grp	12	CAU	EU	– – SR +
Strong et al., 2008	General Med. Dis.	Diag	PST	Ind	10	CAU	EU	+ + SR +
Sudweeks, 1996	Adults	cutoff	CBT	Grp	6	WL	USA	– – SR –
Sudweeks, 1996 hyp	Adults	cutoff	Other	Grp	6	WL	USA	– – SR –
Sudweeks, 1996 h+cbt	Adults	cutoff	CBT	Grp	6	WL	USA	– – SR –
Swartz et al., 2008	Other	Diag	IPT	Ind	8	CAU	USA	– – – –
Talbot et al., 2011	Other	Diag	IPT	Ind	16	CAU	USA	– – – +
Taylor & Marshall, 1977 bat	Students	cutoff	BAT	Ind	6	WL	USA	– – SR –
Taylor, 1977 cbt	Students	cutoff	CBT	Ind	6	WL	USA	– – SR –
Taylor, 1977 ct	Students	cutoff	CBT	Ind	6	WL	USA	– – SR –
Taylor et al., 2009	General Med. Dis.	cutoff	CBT	Ind	15	WL	USA	– – + +
Teasdale, Fennell, Hibbert, & Amies, 1984	Adults	Diag	CBT	Ind	15	CAU	EU	– – SR –
Teichman, Bar-el, Shor, Sirota, & Elizur, 1995	Adults	Diag	CBT	Ind	13	WL	Africa	– – SR –
Teichman, 1995 – CT	Adults	Diag	CBT	Ind	13	WL	Africa	– – SR –
Teri, Logsdon, Uomoto, & McCurry, 1997	General Med. Dis.	Diag	BAT	Ind	9	CAU	USA	– – + –
Teri, 1997 pst	General Med. Dis.	Diag	PST	Ind	9	CAU	USA	– – + –
Titov et al., 2010	Adults	Diag	CBT	Gsh	6	WL	AUS	+ – SR –
Titov, 2010 icbt-ther	Adults	Diag	CBT	Gsh	6	WL	AUS	+ – SR –
Titov et al., 2015	Elderly	Cutoff	CBT	Gsh	5	WL	AUS	+ + SR +
Tovote et al., 2014	General Med. Dis.	cutoff	CBT	Ind	8	WL	EU	+ – – +

continued

Table a. Reference list of randomized trials comparing psychotherapies for adult depression to control groups in Western countries (continued)

Study	Target Group	Diag	Type	Format	Nsess	Control	Region	RoBa)
Tovote, 2014 mbct	General Med. Dis.	cutoff	CBT	Ind	8	WL	EU	+ – – +
Turner, Ward, & Turner, 1979	Adults	cutoff	BAT	Ind	5	Other	USA	– – SR –
Turner, Hambridge, Baker, Bowman, & McElduff, 2013	General Med. Dis.	cutoff	CBT	Grp	6	Other	AUS	+ + SR –
Tyson & Range, 1987	Adults	cutoff	Other	Grp	4	Other	USA	– – SR –
Tyson, 1987 in	Adults	cutoff	Other	Grp	4	Other	USA	– – SR –
Tyson, 1987 tu	Adults	cutoff	Other	Grp	4	Other	USA	– – SR –
Unlu Ince et al., 2013	Other	cutoff	PST	Gsh	5	WL	EU	+ – SR +
van Bastelaar, Pouwer, Cuijpers, Riper, & Snoek, 2011	General Med. Dis.	cutoff	CBT	Gsh	8	WL	EU	+ + SR +
van Schaik et al., 2006	Elderly	Diag	IPT	Ind	10	CAU	EU	+ – – +
Verduyn, Barrowclough, Roberts, Tarrier, & Harrington, 2003 cbt	Other	cutoff	CBT	Grp	16	CAU	EU	– + + –
Verduyn, 2003 sup	Other	cutoff	SUP	Grp	16	CAU	EU	– + + –
Vernmark et al., 2010	Adults	Diag	CBT	Gsh	8	WL	EU	+ + SR +
Vernmark, 2010 gsh	Adults	Diag	CBT	Sh	7	WL	EU	+ + SR +
Vitriol, Ballesteros, Florenzano, Weil, & Benadof, 2009	Other	Diag	DYN	Ind	12	CAU	L-Am	– – + +
Warmerdam, Straten, Twisk, Riper, & Cuijpers, 2008 cbt	Adults	cutoff	CBT	Gsh	8	WL	EU	+ + SR +
Warmerdam, 2008 pst	Adults	cutoff	PST	Gsh	5	WL	EU	+ + SR +
Watkins, Baeyens, & Read, 2009	Adults	cutoff	Other	Ind	8	WL	EU	– – + –
Watkins et al., 2012	Adults	cutoff	Other	Other	4	CAU	EU	+ + + +
Watt & Cappeliez, 2000	Elderly	cutoff	Other	Grp	6	Other	USA	– – + –
Watt, 2000 integr	Elderly	cutoff	Other	Grp	6	Other	USA	– – + –
Weissman et al., 1979	Adults	Diag	IPT	Ind	16	Other	USA	– – + –
Wickberg & Hwang, 1996	Women with PPD	Diag	SUP	Ind	6	CAU	EU	– – + –

continued

Table a. Reference list of randomized trials comparing psychotherapies for adult depression to control groups in Western countries (continued)

Study	Target Group	Diag	Type	Format	Nsess	Control	Region	RoBa)
Wiklund, Mohlkert, & Edman, 2010	Women with PPD	cutoff	CBT	Ind	21	CAU	EU	– – SR –
Williams et al., 2000	Elderly	Diag	PST	Ind	6	Other	USA	+ + + +
Wilson, Goldin, & Charbonneau-Powis, 1983	Adults	cutoff	BAT	Ind	8	WL	AUS	– – – –
Wilson, 1983 cogn	Adults	cutoff	CBT	Ind	8	WL	AUS	– – – –
Wollersheim & Wilson, 1991	Adults	Diag	CBT	Grp	10	WL	USA	– – SR –
Wollersheim, 1991 gsh	Adults	Diag	CBT	Gsh	10	WL	USA	– – SR –
Wollersheim, 1991 sup	Adults	Diag	CBT	Grp	10	WL	USA	– – SR –
Wong, 2008a(Wong, 2008a)	Adults	Diag	CBT	Grp	10	WL	Asia	– + SR +
Wong, 2008b	Adults	Diag	CBT	Grp	10	WL	Asia	– + SR –
Wright et al., 2005	Adults	Diag	CBT	Ind	9	WL	USA	– – + +
Wright, 2005 ccbt	Adults	Diag	CBT	Other	9	WL	USA	– – + +
Wuthrich & Rapee, 2013	Elderly	Diag	CBT	Grp	12	WL	AUS	+ – + +
Zu et al., 2014	Adults	Diag	CBT	Ind	20	CAU	Asia	+ – + –

Note. AUS: Australia; BAT: Behavioral Activation Therapy; CAU: Care as Usual; CBT: Cognitive Behavioral Therapy; Diag: Diagnosis; DYN: Psychodynamic Therapy; EU: Europe; Grp = group format; Gsh = guided self-help format; Ind = individual format; IPT: Interpersonal Psychotherapy; MBCT: Mindfulness Based Cognitive Therapy; Med. Dis.: Medical Disorder; Nsess: Number of sessions; PPD; Post-Partum Depression; PST: Problem-Solving Therapy; RoB: Risk of Bias; SUP: Nondirective Supportive Therapy; tel: Delivered by telephone; USA: North America and Canada; WL: Waitlist.

[a)] In this column a positive (+) or negative (–) sign is given for four quality criteria of the study, respectively: allocation sequence; concealment of allocation to conditions; blinding of assessors; and intention-to-treat analyses. Sr in the third criterion indicates that only self-report measures (and no assessor) were used.

D2. SUPPLEMENTAL MATERIAL

Reference list

Allart-Van Dam, E., Hosman, C. M. H., Hoogduin, C. A. L., & Schaap, C. P. D. R. (2003). The coping with depression course: Short-term outcomes and mediating effects of a randomized controlled trial in the treatment of subclinical depression. *Behavior Therapy*, *34*(3), 381-396.

Ammerman, R. T., Putnam, F. W., Altaye, M., Stevens, J., Teeters, A. R., & Van Ginkel, J. B. (2013). A clinical trial of in-home CBT for depressed mothers in home visitation. *Behavior Therapy*, *44*(3), 359-372.

Andersson, G., Bergstrom, J., Hollandare, F., Carlbring, P., Kaldo, V., & Ekselius, L. (2005). Internet-based self-help for depression: Randomised controlled trial. *British Journal of Psychiatry*, *187*, 456-461.

Arean, P. A., Perri, M. G., Nezu, A. M., Schein, R. L., Christopher, F., & Joseph, T. X. (1993). Comparative effectiveness of social problem-solving therapy and reminiscence therapy as treatments for depression in older adults. *Journal of Consulting and Clinical Psychology*, *61*(6), 1003-1010.

Ayen, I., & Hautzinger, M. (2004). Cognitive behavior therapy for depression in menopausal women. A controlled, randomized treatment study. *Zeitschrift fur Klinische Psychologie und Psychotherapie*, *33*(4), 290-299.

Barber, J. P., Barrett, M. S., Gallop, R., Rynn, M. A., & Rickels, K. (2012). Short-term dynamic psychotherapy versus pharmacotherapy for major depressive disorder: A randomized, placebo-controlled trial. *J Clin Psychiatry*, *73*(1), 66-73.

Barlow, J. (1896). *A group treatment for depression in the elderly*. (unpublished doctoral dissertation), Houston: University of Houston.

Barnhofer, T., Crane, C., Hargus, E., Amarasinghe, M., Winder, R., & Williams, J. M. (2009). Mindfulness-based cognitive therapy as a treatment for chronic depression: A preliminary study. *Behavior Research and Therapy*, *47*(5), 366-373.

Barrera, M. (1979). An evaluation of a brief group therapy for depression. *Journal of Consulting and Clinical Psychology*, *47*(2), 413.

Barrett, J. E., Williams Jr, J. W., Oxman, T. E., Frank, E., Katon, W., Sullivan, M., . . . Sengupta, A. S. (2001). Treatment of dysthymia and minor depression in primary care: A ramdomized trial in patients aged 18 to 59 years. *Journal of Family Practice*, *50*(5), 405-412.

Beach, S. R., & O'Leary, K. D. (1992). Treating depression in the context of marital discord: Outcome and predictors of response of marital therapy versus cognitive therapy. *Behavior Therapy*, *23*(4), 507-528.

Bedard, M., Felteau, M., Marshall, S., Cullen, N., Gibbons, C., Dubois, S., . . . Moustgaard, A. (2014). Mindfulness-based cognitive therapy reduces symptoms of depression in people with a traumatic brain injury: Results from a randomized controlled trial. *Journal of Head Trauma Rehabilitation*, *29*(4), E13-E22.

Beeber, L. S., Holditch-Davis, D., Perreira, K., Schwartz, T. A., Lewis, V., Blanchard, H., . . . Goldman, B. D. (2010). Short-term in-home intervention reduces depressive symptoms in Early Head Start Latina mothers of infants and toddlers. *Research in Nursing and Health*, *33*(1), 60-76.

Berger, T., Hämmerli, K., Gubser, N., Andersson, G., & Caspar, F. (2011). Internet-based treatment of depression: A randomized controlled trial comparing guided with unguided self-help. *Cognitive Behaviour Therapy*, *40*(4), 251-266.

Beutel, M. E., Weissflog, G., Leuteritz, K., Wiltink, J., Haselbacher, A., Ruckes, C., . . . Brahler, E. (2014). Efficacy of short-term psychodynamic psychotherapy (STPP) with depressed breast cancer patients: Results of a randomized controlled multicenter trial. *Annals of Oncology*, *25*(2), 378-384.

Bohlmeijer, E. T., Fledderus, M., Rokx, T. A., & Pieterse, M. E. (2011). Efficacy of an early intervention based on acceptance and commitment therapy for adults with depressive symptomatology: Evaluation in a randomized controlled trial. *Behavior Research and Therapy*, *49*(1), 62-67.

Bolton, P., Bass, J., Neugebauer, R., Verdeli, H., Clougherty, K. F., Wickramaratne, P., . . . Weissman, M. (2003). Group interpersonal psychotherapy for depression in rural Uganda: A randomized controlled trial. *Jama*, *289*(23), 3117-3124.

Bowman, D., Scogin, F., & Lyrene, B. (1995). The efficacy of self-examination therapy and cognitive bibliotherapy in the treatment of mild to moderate depression. *Psychotherapy Research*, *5*(2), 131-140.

Brown, R. A., & Lewinsohn, P. M. (1984). A psychoeducational approach to the treatment of depression: Comparison of group, individual, and minimal contact procedures. *Journal of Consulting and Clinical Psychology*, *52*(5), 774.

Buhrman, M., Syk, M., Burvall, O., Hartig, T., Gordh, T., & Andersson, G. (2015). Individualized guided internet-delivered cognitive-behavior therapy for chronic pain patients with comorbid depression and anxiety: A randomized controlled trial. *Clinical Journal of Pain*, *31*(6), 504-516.

Buntrock, C., Ebert, D., Lehr, D., Riper, H., Smit, F., Cuijpers, P., & Berking, M. (2015). Effectiveness of a web-based cognitive behavioural intervention for subthreshold depression: Pragmatic randomised controlled trial. *Psychotherapy and Psychosomatics*, *84*(6), 348-358.

Burns, A., Banerjee, S., Morris, J., Woodward, Y., Baldwin, R., Proctor, R., . . . Andrew, G. (2007). Treatment and prevention of depression after surgery for hip fracture in older people: Randomized, controlled trials. *Journal of the American Geriatrics Society*, *55*(1), 75-80.

Burns, A., O'Mahen, H., Baxter, H., Bennert, K., Wiles, N., Ramchandani, P., . . . Evans, J. (2013). A pilot randomised controlled trial of cognitive behavioural therapy for antenatal depression. *BMC Psychiatry*, *13*, 33.

Carlbring, P., Hagglund, M., Luthstrom, A., Dahlin, M., Kadowaki, A., Vernmark, K., & Andersson, G. (2013). Internet-based behavioral activation and acceptance-based treatment for depression: A randomized controlled trial. *Journal of Affective Disorders*, *148*(2-3), 331-337.

Carrington, A. (1979). A comparison of cognitive and analytically oriented brief treatment approaches to depression in black women. (unpublished doctoral dissertation), University of Maryland.

Casanas, R., Catalan, R., del Val, J. L., Real, J., Valero, S., & Casas, M. (2012). Effectiveness of a psycho-educational group program for major depression in primary care: A randomized controlled trial. *BMC Psychiatry*, *12*, 230.

Castonguay, L. G., Schut, A. J., Aikens, D. E., Constantino, M. J., Laurenceau, J.-P., Bologh, L., & Burns, D. D. (2004). Integrative cognitive therapy for depression: A preliminary investigation. *Journal of Psychotherapy Integration*, *14*(1), 4-20.

Chan, A. S., Wong, Q. Y., Sze, S. L., Kwong, P. P., Han, Y. M., & Cheung, M. C. (2012). A Chinese Chan-based mind-body intervention for patients with depression. *Journal of Affective Disorders*, *142*(1-3), 283-289.

Chan, M. F., Ng, S. E., Tien, A., Man Ho, R. C., & Thayala, J. (2013). A randomised controlled study to explore the effect of life story review on depression in older Chinese in Singapore. *Health and Social Care in the Community*, *21*(5), 545-553.

Chen, C. H., Tseng, Y. F., Chou, F. H., & Wang, S. Y. (2000). Effects of support group intervention in postnatally distressed women. A controlled study in Taiwan. *Journal of Psychosomatic Research*, *49*(6), 395-399.

Chesney, M. A., Chambers, D. B., Taylor, J. M., Johnson, L. M., & Folkman, S. (2003). Coping effectiveness training for men living with HIV: Results from a randomized clinical trial testing a group-based intervention. *Psychosomatic Medicine*, *65*(6), 1038-1046.

Chiang, K. J., Chen, T. H., Hsieh, H. T., Tsai, J. C., Ou, K. L., & Chou, K. R. (2015). One-year follow-up of the effectiveness of cognitive behavioral group therapy for patients' depression: A randomized, single-blinded, controlled study. *Scientific World Journal*, Article ID 373149.

Cho, H. J., Kwon, J. H., & Lee, J. J. (2008). Antenatal cognitive-behavioral therapy for prevention of postpartum depression: A pilot study. *Yonsei Medical Journal*, *49*(4), 553-562.

Choi, I., Zou, J., Titov, N., Dear, B. F., Li, S., Johnston, L., . . . Hunt, C. (2012). Culturally attuned internet treatment for depression amongst Chinese Australians: A randomised controlled trial. *Journal of Affective Disorders*, *136*(3), 459-468.

Choi, N. G., Marti, C. N., Bruce, M. L., & Hegel, M. T. (2013). Depression in homebound older adults: Problem-solving therapy and personal and social resourcefulness. *Behavior Therapy*, *44*(3), 489-500.

Chronis-Tuscano, A., Clarke, T. L., O'Brien, K. A., Raggi, V. L., Diaz, Y., Mintz, A. D., . . . Thomas, S. R. (2013). Development and preliminary evaluation of an integrated treatment targeting parenting and depressive symptoms in mothers of children with attention-deficit/hyperactivity disorder. *Journal of Consulting and Clinical Psychology*, *81*(5), 918.

Clark, R., Tluczek, A., & Brown, R. (2008). A mother–infant therapy group model for postpartum depression. *Infant Mental Health Journal*, *29*(5), 514-536.

Clark, R., Tluczek, A., & Wenzel, A. (2003). Psychotherapy for postpartum depression: A preliminary report. *American Journal of Orthopsychiatry*, *73*(4), 441-454.

Cohen, S., O'Leary, K. D., & Foran, H. (2010). A randomized clinical trial of a brief, problem-focused couple therapy for depression. *Behavior Therapy*, *41*(4), 433-446.

Cooper, P. J., Murray, L., Wilson, A., & Romaniuk, H. (2003). Controlled trial of the short- and long-term effect of psychological treatment of post-partum depression. I. Impact on maternal mood. *British Journal of Psychiatry*, *182*, 412-419.

Cramer, H., Salisbury, C., Conrad, J., Eldred, J., & Araya, R. (2011). Group cognitive behavioural therapy for women with depression: Pilot and feasibility study for a randomised controlled trial using mixed methods. *BMC Psychiatry*, *11*, 82.

Cullen, J. (2002). Testing the effectiveness of behavioral activation therapy in the treatment of acute unipolar depression. (unpublished doctoral dissertation.), Western Michigan University.

Dekker, R. L., Moser, D. K., Peden, A. R., & Lennie, T. A. (2012). Cognitive therapy improves three-month outcomes in hospitalized patients with heart failure. *Journal of Cardial Failure*, *18*(1), 10-20.

DeRubeis, R. J., Hollon, S. D., Amsterdam, J. D., Shelton, R. C., Young, P. R., Salomon, R. M., . . . Gallop, R. (2005). Cognitive therapy vs medications in the treatment of moderate to severe depression. *Archives of General Psychiatry*, *62*(4), 409-416.

Dimidjian, S., Hollon, S. D., Dobson, K. S., Schmaling, K. B., Kohlenberg, R. J., Addis, M. E., . . . Jacobson, N. S. (2006). Randomized trial of behavioral activation, cognitive therapy, and antidepressant medication in the acute treatment of adults with major depression. *Journal of Consulting and Clinical Psychology, 74*(4), 658-670.

Dindo, L., Recober, A., Marchman, J. N., Turvey, C., & O'Hara, M. W. (2012). One-day behavioral treatment for patients with comorbid depression and migraine: A pilot study. *Behaviour Research and Therapy, 50*(9), 537-543.

Dobkin, R. D., Menza, M., Allen, L. A., Gara, M. A., Mark, M. H., Tiu, J., . . . Friedman, J. (2011). Cognitive-behavioral therapy for depression in Parkinson's disease: A randomized, controlled trial. *American Journal of Psychiatry, 168*(10), 1066-1074.

Doering, L. V., Chen, B., Cross Bodan, R., Magsarili, M. C., Nyamathi, A., & Irwin, M. R. (2013). Early cognitive behavioral therapy for depression after cardiac surgery. *Journal of Cardiovascular Nursing, 28*(4), 370-379.

Dowrick, C., Dunn, G., Ayuso-Mateos, J. L., Dalgard, O. S., Page, H., & Lehtinen, V. (2000). Problem solving treatment and group psychoeducation for depression: Multicentre randomised controlled trial Outcomes of Depression International Network [ODIN] Group. *British Medical Journal, 321*(7274), 1450-1454.

Duarte, P. S., Miyazaki, M. C., Blay, S. L., & Sesso, R. (2009). Cognitive-behavioral group therapy is an effective treatment for major depression in hemodialysis patients. *Kidney International, 76*(4), 414-421.

Duchac, N. (2002). The use of a rational emotive behavioral therapy to treat depression with incarcerated males. (unpublished doctoral dissertation.), University of Toledo.

Dwight-Johnson, M., Aisenberg, E., Golinelli, D., Hong, S., O'Brien, M., & Ludman, E. (2011). Telephone-based cognitive-behavioral therapy for Latino patients living in rural areas: A randomized pilot study. *Psychiatric Services, 62*(8), 936-942.

Ekers, D., Richards, D., McMillan, D., Bland, J. M., & Gilbody, S. (2011). Behavioural activation delivered by the non-specialist: Phase II randomised controlled trial. *British Journal of Psychiatry, 198*(1), 66-72.

Elkin, I., Shea, M. T., Watkins, J. T., Imber, S. D., Sotsky, S. M., Collins, J. F., . . . et al. (1989). National institute of mental health treatment of depression collaborative research program. General effectiveness of treatments. *Archives of General Psychiatry, 46*(11), 971-982; discussion 983.

Epstein, D. (1986). Aerobic activity versus group cognitive therapy: An evaluative study of contrasting interventions for the alleviation of clinical depression. (unpublished doctoral dissertation.), University of Nevada, Reno.

Evans, R. L., & Connis, R. T. (1995). Comparison of brief group therapies for depressed cancer patients receiving radiation treatment. *Public Health Reports, 110*(3), 306-311.

Fann, J. R., Bombardier, C. H., Vannoy, S., Dyer, J., Ludman, E., Dikmen, S., . . . Temkin, N. (2015). Telephone and in-person cognitive behavioral therapy for major depression after traumatic brain injury: A randomized controlled trial. *J Neurotrauma, 32*(1), 45-57.

Faramarzi, M., Alipor, A., Esmaelzadeh, S., Kheirkhah, F., Poladi, K., & Pash, H. (2008). Treatment of depression and anxiety in infertile women: Cognitive behavioral therapy versus fluoxetine. *Journal of Affective Disorders, 108*(1-2), 159-164.

Fledderus, M., Bohlmeijer, E. T., Pieterse, M. E., & Schreurs, K. M. (2012). Acceptance and commitment therapy as guided self-help for psychological distress and positive mental health: A randomized controlled trial. *Psychological Medicine, 42*(3), 485-495.

Floyd, M., Scogin, F., McKendree-Smith, N. L., Floyd, D. L., & Rokke, P. D. (2004). Cognitive therapy for depression a comparison of individual psychotherapy and bibliotherapy for depressed older adults. *Behavior Modification*, *28*(2), 297-318.

Folke, F., Parling, T., & Melin, L. (2012). Acceptance and commitment therapy for depression: A preliminary randomized clinical trial for unemployed on long-term sick leave. *Cognitive and Behavioral Practice*, *19*(4), 583-594.

Forsyth, K. (2000). *The design and implementation of a depression prevention program*. (unpublished doctoral dissertation.), University of Rhode Island.

Freedland, K. E., Carney, R. M., Rich, M. W., Steinmeyer, B. C., & Rubin, E. H. (2015). Cognitive behavior therapy for depression and self-care in heart failure patients a randomized clinical trial. *JAMA Internal Medicine*, *175*(11), 1773-1782.

Freedland, K. E., Skala, J. A., Carney, R. M., Rubin, E. H., Lustman, P. J., D·vila-Rom·n, V. G., . . . Hogue, C. W. (2009). Treatment of depression after coronary artery bypass surgery: A randomized controlled trial. *Archives of General Psychiatry*, *66*(4), 387-396.

Frothingham, S. (2005). The effects of an optimism-based cognitive behavioral intervention on mood and functioning in cardiac patients. (unpublished doctoral dissertation.), University of Southern Mississippi.

Fry, P. (1983). Structured and unstructured reminiscence training and depression among the elderly. *Clinical Gerontologist*, *1*(3), 15-37.

Furukawa, T. A., Horikoshi, M., Kawakami, N., Kadota, M., Sasaki, M., Sekiya, Y., . . . Grothaus, L. C. (2012). Telephone cognitive-behavioral therapy for subthreshold depression and presenteeism in workplace: A randomized controlled trial. *PLoS ONE*, *7*(4), e35330.

García-Peña, C., Vázquez-Estupiñan, F., Avalos-Pérez, F., Jiménez, L. V. R., Sánchez-Garcia, S., & Juárez-Cedillo, T. (2015). Clinical effectiveness of group cognitive-behavioural therapy for depressed older people in primary care: A randomised controlled trial. *Salud Mental*, *38*(1), 33-39.

Gawrysiak, M., Nicholas, C., & Hopko, D. R. (2009). Behavioral activation for moderately depressed university students: Randomized controlled trial. *Journal of Counseling Psychology*, *56*(3), 468-475.

Gehr, P. (1988). *Guided imagery as a treatment intervention for depression*. (unpublished doctoral dissertation.), United States International University.

Gellis, Z. D., & Bruce, M. L. (2010). Problem solving therapy for subthreshold depression in home healthcare patients with cardiovascular disease. *American Journal of Geriatric Psychiatry*, *18*(6), 464-474.

Geraedts, A. S., Kleiboer, A. M., Wiezer, N. M., van Mechelen, W., & Cuijpers, P. (2014). Short-term effects of a web-based guided self-help intervention for employees with depressive symptoms: Randomized controlled trial. *Journal of Medical Internet Research*, *16*(5), e121.

Gitlin, L. N., Harris, L. F., McCoy, M. C., Chernett, N. L., Pizzi, L. T., Jutkowitz, E., . . . Hauck, W. W. (2013). A home-based intervention to reduce depressive symptoms and improve quality of life in older African Americans: A randomized trial. *Annals of Internal Medicine*, *159*(4), 243-252.

Goodman, J. H., Prager, J., Goldstein, R., & Freeman, M. (2015). Perinatal dyadic psychotherapy for postpartum depression: A randomized controlled pilot trial. *Archives of Womens Mental Health*, *18*(3), 493-506.

Grote, N. K., Swartz, H. A., Geibel, S. L., Zuckoff, A., Houck, P. R., & Frank, E. (2009). A randomized controlled trial of culturally relevant, brief interpersonal psychotherapy for perinatal depression. *Psychiatric Services*, *60*(3), 313-321.

Hallgren, M., Kraepelien, M., Öjehagen, A., Lindefors, N., Zeebari, Z., Kaldo, V., & Forsell, Y. (2015). Physical exercise and internet-based cognitive-behavioural therapy in the treatment of depression: Randomised controlled trial. *British Journal of Psychiatry*, *207*(3), 227-234.

Hamamci, Z. (2006). Integrating psychodrama and cognitive behavioral therapy to treat moderate depression. *Arts in Psychotherapy*, *33*(3), 199-207.

Hamdan-Mansour, A. M., Puskar, K., & Bandak, A. G. (2009). Effectiveness of cognitive-behavioral therapy on depressive symptomatology, stress and coping strategies among Jordanian university students. *Issues in Mental Health Nursing*, *30*(3), 188-196.

Haringsma, R., Engels, G., Cuijpers, P., & Spinhoven, P. (2006). Effectiveness of the Coping With Depression (CWD) course for older adults provided by the community-based mental health care system in the Netherlands: A randomized controlled field trial. *International Psychogeriatrics*, *18*(02), 307-325.

Harley, R., Sprich, S., Safren, S., Jacobo, M., & Fava, M. (2008). Adaptation of dialectical behavior therapy skills training group for treatment-resistant depression. The *Journal of Nervous and Mental Disease*, *196*(2), 136-143.

Hassiotis, A., Serfaty, M., Azam, K., Strydom, A., Blizard, R., Romeo, R., . . . King, M. (2013). Manualised individual cognitive behavioural therapy for mood disorders in people with mild to moderate intellectual disability: A feasibility randomised controlled trial. *Journal of Affective Disorders*, *151*(1), 186-195.

Hautzinger, M., & Welz, S. (2004). Cognitive behavioral therapy for depressed older outpatients: A controlled, randomized trial. *Zeitschrift für Gerontologie und Geriatrie*, *37*(6), 427-435.

Hayman, P. M., & Cope, C. S. (1980). Effects of assertion training on depression. *Journal of Clinical Psychology*, *36*(2), 534-543.

Heckman, T. G., Sikkema, K. J., Hansen, N., Kochman, A., Heh, V., Neufeld, S., . . . Group, A. R. (2011). A randomized clinical trial of a coping improvement group intervention for HIV-infected older adults. *Journal of Behavioral Medicine*, *34*(2), 102-111.

Hegerl, U., Hautzinger, M., Mergl, R., Kohnen, R., Sch¸tze, M., Scheunemann, W., . . . Henkel, V. (2010). Effects of pharmacotherapy and psychotherapy in depressed primary-care patients: A randomized, controlled trial including a patients' choice arm. *International Journal of Neuropsychopharmacology*, *13*(1), 31-44.

Hermanns, N., Schmitt, A., Gahr, A., Herder, C., Nowotny, B., Roden, M., . . . Kulzer, B. (2015). The effect of a diabetes-specific cognitive behavioral treatment program (DIAMOS) for patients with diabetes and subclinical depression: Results of a randomized controlled trial. *Diabetes Care*, *38*(4), 551-560.

Hogg, J. A., & Deffenbacher, J. L. (1988). A comparison of cognitive and interpersonal-process group therapies in the treatment of depression among college students. *Journal of Counseling Psychology*, *35*(3), 304.

Holden, J. M., Sagovsky, R., & Cox, J. L. (1989). Counselling in a general practice setting: Controlled study of heath visitor intervention in treatment of postnatal depression. *British Medical Journal*, *298*(6668), 223-226.

Honey, K. L., Bennett, P., & Morgan, M. (2002). A brief psycho-educational group intervention for postnatal depression. *British Journal of Clinical Psychology*, *41*(4), 405-409.

Horrell, L., Goldsmith, K. A., Tylee, A. T., Schmidt, U. H., Murphy, C. L., Bonin, E.-M., . . . Brown, J. S. L. (2014). One-day cognitive–behavioural therapy self-confidence workshops for people with depression: Randomised controlled trial. *The British Journal of Psychiatry*, *204*(3), 222-233.

Hou, Y., Hu, P., Zhang, Y., Lu, Q., Wang, D., Yin, L., . . . Zou, X. (2014). Cognitive behavioral therapy in combination with systemic family therapy improves mild to moderate postpartum depression. *Rev Bras Psiquiatr*, *36*(1), 47-52.

Huang, C. Y., Lai, H. L., Chen, C. I., Lu, Y. C., Li, S. C., Wang, L. W., & Su, Y. (2015). Effects of motivational enhancement therapy plus cognitive behaviour therapy on depressive symptoms and health-related quality of life in adults with type II diabetes mellitus: A randomised controlled trial. *Quality of Life Research*, *25*(5), 1275.

Hunter, S. B., Witkiewitz, K., Watkins, K. E., Paddock, S. M., & Hepner, K. A. (2012). The moderating effects of group cognitive–behavioral therapy for depression among substance users. *Psychology of Addictive Behaviors*, *26*(4), 906-916.

Jamison, C., & Scogin, F. (1995). The outcome of cognitive bibliotherapy with depressed adults. *Journal of Consulting and Clinical Psychology*, *63*(4), 644-650.

Jarrett, R. B., Schaffer, M., McIntire, D., Witt-Browder, A., Kraft, D., & Risser, R. C. (1999). Treatment of atypical depression with cognitive therapy or phenelzine: A double-blind, placebo-controlled trial. *Archives of General Psychiatry*, *56*(5), 431-437.

Jesse, D. E., Gaynes, B. N., Feldhousen, E. B., Newton, E. R., Bunch, S., & Hollon, S. D. (2015). Performance of a culturally tailored cognitive-behavioral intervention integrated in a public health setting to reduce risk of antepartum depression: A randomized controlled trial. *Journal of Midwifery and Women's Health*, *60*(5), 578-592.

Jiang, L., Wang, Z. Z., Qiu, L. R., Wan, G. B., Lin, Y., & Wei, Z. (2014). Psychological intervention for postpartum depression. *Journal of Huazhong University of Science and Technology [Medical Sciences]*, *34*(3), 437-442.

Johansson, R., Ekbladh, S., Hebert, A., Lindström, M., Möller, S., Petitt, E., . . . Andersson, G. (2012). Psychodynamic guided self-help for adult depression through the internet: A randomised controlled trial. *PLoS ONE*, *7*(5), e38021.

Johansson, R., Sjöberg, E., Sjögren, M., Johnsson, E., Carlbring, P., Andersson, T., . . . Andersson, G. (2012). Tailored vs. standardized internet-based cognitive behavior therapy for depression and comorbid symptoms: A randomized controlled trial. *PLoS ONE*, *7*(5), e36905.

Johnson, J. E., & Zlotnick, C. (2012). Pilot study of treatment for major depression among women prisoners with substance use disorder. *Journal of Psychiatric Research*, *46*(9), 1174-1183.

Joling, K. J., Hout, H. P., van't Veer-Tazelaar, P. J., Horst, H. E., Cuijpers, P., Ven, P. M., & Marwijk, H. W. (2011). How effective is bibliotherapy for very old adults with subthreshold depression? A randomized controlled trial. *American Journal of Geriatric Psychiatry*, *19*(3), 256-265.

Kanter, J. W., Santiago-Rivera, A. L., Santos, M. M., Nagy, G., López, M., Hurtado, G. D., & West, P. (2015). A randomized hybrid efficacy and effectiveness trial of behavioral activation for latinos with depression. *Behavior Therapy*, *46*(2), 177-192.

Kelly, J. A., Murphy, D. A., Bahr, G. R., Kalichman, S. C., Morgan, M. G., Stevenson, L. Y., . . . Bernstein, B. M. (1993). Outcome of cognitive-behavioral and support group brief therapies for depressed, HIV-infected persons. *American Journal of Psychiatry*, *150*(11), 1679-1686.

Kessler, D., Lewis, G., Kaur, S., Wiles, N., King, M., Weich, S., . . . Peters, T. J. (2009). Therapist-delivered Internet psychotherapy for depression in primary care: A randomised controlled trial. *Lancet*, *374*(9690), 628-634.

King, M., Sibbald, B., Ward, E., Bower, P., Lloyd, M., Gabbay, M., & Byford, S. (2000). Randomised controlled trial of non-directive counselling, cognitive-behaviour therapy and usual general practitioner care in the management of depression as well as mixed anxiety and depression in primary care. *Health Technol Assess*, *4*(19), 1-83.

Kivi, M., Eriksson, M. C. M., Hange, D., Petersson, E.-L., Vernmark, K., Johansson, B., & Björkelund, C. (2014). Internet-based therapy for mild to moderate depression in Swedish primary care: Short term results from the PRIM-NET randomized controlled trial. *Cognitive Behaviour Therapy*, *43*(4), 289-298.

Kleiboer, A., Donker, T., Seekles, W., van Straten, A., Riper, H., & Cuijpers, P. (2015). A randomized controlled trial on the role of support in Internet-based problem solving therapy for depression and anxiety. *Behaviour Research and Therapy*, *72*, 63-71.

Korrelboom, K., Maarsingh, M., & Huijbrechts, I. (2012). Competitive memory training (COMET) for treating low self-esteem in patients with depressive disorders: A randomized clinical trial. *Depression and Anxiety*, *29*(2), 102-110.

Korte, J., Bohlmeijer, E. T., Cappeliez, P., Smit, F., & Westerhof, G. J. (2012). Life review therapy for older adults with moderate depressive symptomatology: A pragmatic randomized controlled trial. *Psychological Medicine*, *42*(6), 1163-1173.

Krampen, G. (1997). Application of autogenic training before and in addition to integrative psychotherapy of depressive disorders. *Zeitschrift Fur Klinische Psychologie, Psychiatrie Und Psychotherapie*, *45*(2), 214-232.

Laidlaw, K., Davidson, K., Toner, H., Jackson, G., Clark, S., Law, J., . . . Cross, S. (2008). A randomised controlled trial of cognitive behaviour therapy vs treatment as usual in the treatment of mild to moderate late life depression. *International Journal of Geriatric Psychiatry*, *23*(8), 843-850.

Lamers, F., Jonkers, C. C., Bosma, H., Kempen, G. I., Meijer, J. A., Penninx, B. W., . . . van Eijk, J. T. (2010). A minimal psychological intervention in chronically ill elderly patients with depression: A randomized trial. *Psychotherapy and Psychosomatics*, *79*(4), 217-226.

Lamers, S. M., Bohlmeijer, E. T., Korte, J., & Westerhof, G. J. (2015). The efficacy of life-review as online-guided self-help for adults: A randomized trial. *Journal of Gerontology Series B: Psychological Sciences and Social Sciences*, *70*(1), 24-34.

Landreville, P., & Bissonnette, L. (1997). Effects of cognitive bibliotherapy for depressed older adults with a disability. *Clinical Gerontologist*, *17*(4), 35-55.

Lappalainen, P., Langrial, S., Oinas-Kukkonen, H., Tolvanen, A., & Lappalainen, R. (2015). Web-based acceptance and commitment therapy for depressive symptoms with minimal support: A randomized controlled trial. *Behavior Modification*, *39*(6), 805-834.

Larcombe, N. A., & Wilson, P. H. (1984). An evaluation of cognitive-behaviour therapy for depression in patients with multiple sclerosis. *British Journal of Psychiatry*, *145*, 366-371.

Lemma, A., & Fonagy, P. (2013). Feasibility study of a psychodynamic online group intervention for depression. *Psychoanalytic Psychology*, *30*(3), 367-380.

Leung, S. S., Lee, A. M., Chiang, V. C., Lam, S., Kuen, Y. W., & Wong, D. F. (2013). Culturally sensitive, preventive antenatal group cognitive–behavioural therapy for Chinese women with depression. *International Journal of Nursing Practice*, *19*(S1), 28-37.

Lexis, M. A., Jansen, N. W., Huibers, M. J., Amelsvoort, L. G., Berkouwer, A., Tjin, A. T. G., . . . Kant, I. (2011). Prevention of long-term sickness absence and major depression in high-risk employees: A randomised controlled trial. *Occupational and Environmental Medicine*, *68*(6), 400-407.

Linde, J. A., Simon, G. E., Ludman, E. J., Ichikawa, L. E., Operskalski, B. H., Arterburn, D., … Jeffery, R. W. (2011). A randomized controlled trial of behavioral weight loss treatment versus combined weight loss/depression treatment among women with comorbid obesity and depression. *Annals of Behavioral Medicine*, *41*(1), 119-130.

Liu, E. T.-H., Chen, W.-L., Li, Y.-H., Wang, C. H., Mok, T. J., & Huang, H. S. (2009). Exploring the efficacy of cognitive bibliotherapy and a potential mechanism of change in the treatment of depressive symptoms among the Chinese: A randomized controlled trial. *Cognitive Therapy and Research*, *33*(5), 449-461.

Losada, A., Márquez-González, M., Romero-Moreno, R., Mausbach, B. T., López, J., Fernández-Fernández, V., & Nogales-González, C. (2015). Cognitive–behavioral therapy (CBT) versus acceptance and commitment therapy (ACT) for dementia family caregivers with significant depressive symptoms: Results of a randomized clinical trial. *Journal of Consulting and Clinical Psychology*, *83*(4), 760-772.

Lovell, K., Bower, P., Richards, D., Barkham, M. i., Sibbald, B., Roberts, C., … Hennessy, S. (2008). Developing guided self-help for depression using the medical research council complex interventions framework: A description of the modelling phase and results of an exploratory randomised controlled trial. *BMC Psychiatry*, *8*(1), 91.

Lustman, P. J., Griffith, L. S., Freedland, K. E., Kissel, S. S., & Clouse, R. E. (1998). Cognitive behavior therapy for depression in type 2 diabetes mellitus. A randomized, controlled trial. *Annals of Internal Medicine*, *129*(8), 613-621.

Lynch, D., Tamburrino, M., Nagel, R., & Smith, M. K. (2004). Telephone-based treatment for family practice patients with mild depression. *Psychological Reports*, *94*(3 Pt 1), 785-792.

Lynch, D. J., Tamburrino, M. B., & Nagel, R. (1997). Telephone counseling for patients with minor depression: Preliminary findings in a family practice setting. *Journal of Family Practice*, *44*(3), 293-298.

MacPherson, H., Richmond, S., Bland, M., Brealey, S., Gabe, R., Hopton, A., … Watt, I. (2013). Acupuncture and counselling for depression in primary care: A randomised controlled trial. *PLoS Med*, *10*(9), e1001518.

Maina, G., Forner, F., & Bogetto, F. (2005). Randomized controlled trial comparing brief dynamic and supportive therapy with waiting list condition in minor depressive disorders. *Psychotherapy and Psychosomatics*, *74*(1), 43-50.

Malouff, J. M., Lanyon, R. I., & Schutte, N. S. (1988). Effectiveness of a brief group RET treatment for divorce-related dysphoria. *Journal of Rational-Emotive and Cognitive-Behavior Therapy*, *6*(3), 162-171.

Martin, P. R., Aiello, R., Gilson, K., Meadows, G., Milgrom, J., & Reece, J. (2015). Cognitive behavior therapy for comorbid migraine and/or tension-type headache and major depressive disorder: An exploratory randomized controlled trial. *Behaviour Research and Therapy*, *73*, 8-18.

McClay, C.-A., Collins, K., Matthews, L., Haig, C., McConnachie, A., Morrison, J., … McAnee, G. (2015). A community-based pilot randomised controlled study of life skills classes for individuals with low mood and depression. *BMC Psychiatry*, *15*(1), 1.

McKee, M. D., Zayas, L. H., Fletcher, J., Boyd, R. C., & Nam, S. H. (2006). Results of an intervention to reduce perinatal depression among low-income minority women in community primary care. *Journal of Social Service Research*, *32*(4), 63-81.

McKendree-Smith, N. L. (1998). Cognitive and behavioral bibliotherapy for depression: An examination of efficacy and mediators and moderators of change. (unpublished Doctiral Dissertation), The University of Alabama.

Michalak, J., Schultze, M., Heidenreich, T., & Schramm, E. (2015). A randomized controlled trial on the efficacy of mindfulness-based cognitive therapy and a group version of cognitive behavioral analysis system of psychotherapy for chronically depressed patients. *Journal of Consulting and Clinical Psychology*, *83*(5), 951-963.

Milgrom, J., Holt, C., Holt, C. J., Ross, J., Ericksen, J., & Gemmill, A. W. (2015). Feasibility study and pilot randomised trial of an antenatal depression treatment with infant follow-up. *Archives of Womens Mental Health*, *18*(5), 717-730.

Milgrom, J., Holt, C. J., Gemmill, A. W., Ericksen, J., Leigh, B., Buist, A., & Schembri, C. (2011). Treating postnatal depressive symptoms in primary care: A randomised controlled trial of GP management, with and without adjunctive counselling. *BMC Psychiatry*, *11*, 95.

Milgrom, J., Negri, L. M., Gemmill, A. W., McNeil, M., & Martin, P. R. (2005). A randomized controlled trial of psychological interventions for postnatal depression. *British Journal of Clinical Psychology*, *44*(Pt 4), 529-542.

Miller, L., & Weissman, M. (2002). Interpersonal psychotherapy delivered over the telephone to recurrent depressives. A pilot study. *Depression and Anxiety*, *16*(3), 114-117.

Miranda, J., Chung, J. Y., Green, B. L., Krupnick, J., Siddique, J., Revicki, D. A., & Belin, T. (2003). Treating depression in predominantly low-income young minority women: A randomized controlled trial. *Jama*, *290*(1), 57-65.

Mohr, D. C., Carmody, T., Erickson, L., Jin, L., & Leader, J. (2011). Telephone-administered cognitive behavioral therapy for veterans served by community-based outpatient clinics. *Journal of Consulting and Clinical Psychology*, *79*(2), 261-265.

Mohr, D. C., Duffecy, J., Ho, J., Kwasny, M., Cai, X., Burns, M. N., & Begale, M. (2013). A randomized controlled trial evaluating a manualized TeleCoaching protocol for improving adherence to a web-based intervention for the treatment of depression. *PLoS ONE*, *8*(8), e70086.

Mohr, D. C., Likosky, W., Bertagnolli, A., Goodkin, D. E., Van Der Wende, J., Dwyer, P., & Dick, L. P. (2000). Telephone-administered cognitive-behavioral therapy for the treatment of depressive symptoms in multiple sclerosis. *Journal of Consulting and Clinical Psychology*, *68*(2), 356-361.

Moldovan, R., Cobeanu, O., & David, D. (2013). Cognitive bibliotherapy for mild depressive symptomatology: Randomized clinical trial of efficacy and mechanisms of change. *Clinical Psychology and Psychotherapy*, *20*(6), 482-493.

Morris, N. (1975). A group self-instruction method for the treatment of depressed outpatients. (doctoral dissertation), University of Toronto.

Mossey, J. M., Knott, K. A., Higgins, M., & Talerico, K. (1996). Effectiveness of a psychosocial intervention, interpersonal counseling, for subdysthymic depression in medically ill elderly. The *Journals of Gerontology series A: Biological Sciences and Medical Sciences*, *51*(4), M172-178.

Mukhtar, F. (2011). Predictors of group cognitive behaviour therapy outcomes for the treatment of depression in malaysia. *Asian Journal of Psychiatry*, *4*(2), 125-128.

Mulcahy, R., Reay, R. E., Wilkinson, R. B., & Owen, C. (2010). A randomised control trial for the effectiveness of group interpersonal psychotherapy for postnatal depression. *Archives of Womens Mental Health*, *13*(2), 125-139.

Mynors-Wallis, L., Gath, D., Lloyd-Thomas, A., & Tomlinson, D. (1995). Randomised controlled trial comparing problem solving treatment with amitriptyline and placebo for major depression in primary care. *Bmj*, *310*(6977), 441-445.

Naeem, F., Sarhandi, I., Gul, M., Khalid, M., Aslam, M., & Anbrin, A. (2014). A multicentre randomised controlled trial of a carer supervised culturally adapted cbt (cacbt) based self-help for depression in pakistan. *Journal of Affective Disorders*, *156*, 224-227

Nakimuli-Mpungu, E., Wamala, K., Okello, J., Alderman, S., Odokonyero, R., Mojtabai, R., . . . Musisi, S. (2015). Group support psychotherapy for depression treatment in people with HIV/AIDS in northern Uganda: A single-centre randomised controlled trial. *The Lancet HIV*, *2*(5), e190-e199.

Neugebauer, R., Kline, J., Markowitz, J. C., Bleiberg, K. L., Baxi, L., Rosing, M. A., . . . Keith, J. (2006). Pilot randomized controlled trial of interpersonal counseling for subsyndromal depression following miscarriage. *Journal of Clinical Psychiatry*, *67*(8), 1299-1304.

Nezu, A. M. (1986). Efficacy of a social problem-solving therapy approach for unipolar depression. *Journal of Consulting and Clinical Psychology*, *54*(2), 196-202.

Nezu, A. M., & Perri, M. G. (1989). Social problem-solving therapy for unipolar depression: An initial dismantling investigation. *Journal of Consulting and Clinical Psychology*, *57*(3), 408-413.

Ng, S. E., Tien, A., Thayala, J. N., Ho, R. C., & Chan, M. F. (2013). The effect of life story review on depression of older community-dwelling Chinese adults in Singapore: A preliminary result. *International Journal of Geriatric Psychiatry*, *28*(3), 328-330.

Ngai, F. W., Wong, P.-C., Leung, K. Y., Chau, P. H., & Chung, K. F. (2015). The effect of telephone-based cognitive-behavioral therapy on postnatal depression: A randomized controlled trial. *Psychotherapy and Psychosomatics*, *84*(5), 294-303.

Nobis, S., Lehr, D., Ebert, D. D., Baumeister, H., Snoek, F., Riper, H., & Berking, M. (2015). Efficacy of a web-based intervention with mobile phone support in treating depressive symptoms in adults with type 1 and type 2 diabetes: A randomized controlled trial. *Diabetes Care*, *38*(5), 776-783.

O'Hara, M. W., Stuart, S., Gorman, L. L., & Wenzel, A. (2000). Efficacy of interpersonal psychotherapy for postpartum depression. *Archives of General Psychiatry*, *57*(11), 1039-1045.

O'Mahen, H., Himle, J. A., Fedock, G., Henshaw, E., & Flynn, H. (2013). A pilot randomized controlled trial of cognitive behavioral therapy for perinatal depression adapted for women with low incomes. *Depression and Anxiety*, *30*(7), 679-687.

O'Mahen, H. A., Woodford, J., McGinley, J., Warren, F. C., Richards, D. A., Lynch, T. R., & Taylor, R. S. (2013). Internet-based behavioral activation-treatment for postnatal depression (Netmums): A randomized controlled trial. *Journal of Affective Disorders*, *150*(3), 814-822.

O'Neil, A., Taylor, B., Sanderson, K., Cyril, S., Chan, B., Hawkes, A. L., . . . Atherton, J. J. (2014). Efficacy and feasibility of a tele-health intervention for acute coronary syndrome patients with depression: Results of the "MoodCare" randomized controlled trial. *Annals of Behavioral Medicine*, *48*(2), 163-174.

Omidi, A., Mohammadkhani, P., Mohammadi, A., & Zargar, F. (2013). Comparing mindfulness based cognitive therapy and traditional cognitive behavior therapy with treatments as usual on reduction of major depressive disorder symptoms. *Iranian Red Crescent Medical Journal*, *15*(2), 142-146.

Pace, T. M., & Dixon, D. N. (1993). Changes in depressive self-schemata and depressive symptoms following cognitive therapy. *Journal of Counseling Psychology*, *40*(3), 288.

Pagoto, S., Schneider, K. L., Whited, M. C., Oleski, J. L., Merriam, P., Appelhans, B., . . . Crawford, S. (2013). Randomized controlled trial of behavioral treatment for comorbid obesity and depression in women: The be active trial. *International Journal of Obesity*, *37*(11), 1427-1434.

Pecheur, D. R., & Edwards, K. J. (1984). A comparison of secular and religious versions of cognitive therapy with depressed christian college students. *Journal of Psychology and Theology*, *12*(1), 54-54.

Peden, A. R., Hall, L. A., Rayens, M. K., & Beebe, L. L. (2000). Reducing negative thinking and depressive symptoms in college women. *Journal of Nursing Scholarship*, *32*(2), 145-151.

Penckofer, S. M., Ferrans, C., Mumby, P., Byrn, M., Emanuele, M. A., Harrison, P. R., . . . Lustman, P. (2012). A psychoeducational intervention (SWEEP) for depressed women with diabetes. *Annals of Behavioral Medicine*, *44*(2), 192-206.

Perini, S., Titov, N., & Andrews, G. (2009). Clinician-assisted Internet-based treatment is effective for depression: Randomized controlled trial. *Australian and New Zealand Journal of Psychiatry*, *43*(6), 571-578.

Petersen, I., Hanass Hancock, J., Bhana, A., & Govender, K. (2014). A group-based counselling intervention for depression comorbid with HIV/AIDS using a task shifting approach in South Africa: A randomized controlled pilot study. *Journal of Affective Disorders*, *158*, 78-84.

Pibernik-Okanovic, M., Begic, D., Ajdukovic, D., Andrijasevic, N., & Metelko, Z. (2009). Psychoeducation versus treatment as usual in diabetic patients with subthreshold depression: Preliminary results of a randomized controlled trial. *Trials*, *10*, 78.

Poleshuck, E. L., Gamble, S. A., Bellenger, K., Lu, N., Tu, X., Sorensen, S., . . . Talbot, N. L. (2014). Randomized controlled trial of interpersonal psychotherapy versus enhanced treatment as usual for women with co-occurring depression and pelvic pain. *Journal of Psychosomatic Research*, *77*(4), 264-272.

Pot, A. M., Bohlmeijer, E. T., Onrust, S., Melenhorst, A.-S., Veerbeek, M., & De Vries, W. (2010). The impact of life review on depression in older adults: A randomized controlled trial. *International Psychogeriatrics*, *22*(4), 572-581.

Pots, W. T. M., Meulenbeek, P. A. M., Veehof, M. M., Klungers, J., & Bohlmeijer, E. T. (2014). The efficacy of mindfulness-based cognitive therapy as a public mental health intervention for adults with mild to moderate depressive symptomatology: A randomized controlled trial. *PLoS ONE*, *9*(10), e109789.

Power Michael, J., & Freeman, C. (2012). A randomized controlled trial of IPT versus CBT in primary care: With some cautionary notes about handling missing values in clinical trials. *Clinical Psychology and Psychotherapy*, *19*(2), 159-169.

Prendergast, J., & Austin, M. P. (2001). Early childhood nurse-delivered cognitive behavioural counselling for post-natal depression. *Australasian Psychiatry*, *9*(3), 255-259.

Preschl, B., Maercker, A., Wagner, B., Forstmeier, S., Banos, R. M., Alcaniz, M., . . . Botella, C. (2012). Life-review therapy with computer supplements for depression in the elderly: A randomized controlled trial. *Aging and Mental Health*, *16*(8), 964-974.

Propst, L. R., Ostrom, R., Watkins, P., Dean, T., & Mashburn, D. (1992). Comparative efficacy of religious and nonreligious cognitive-behavioral therapy for the treatment of clinical depression in religious individuals. *Journal of Consulting and Clinical Psychology*, *60*(1), 94-103.

Puckering, C., McIntosh, E., Hickey, A., & Longford, J. (2010). Mellow Babies: A group intervention for infants and mothers experiencing postnatal depression. *Counselling Psychology Review*, *25*(1), 28-38.

Pugh, N. E. (2014). A Randomized Controlled Trial of a Therapist-Assisted Internet Cognitive Behaviour Therapy Program for Women with Postpartum Depression. (doctoral dissertatino) Faculty of Graduate Studies and Research, University of Regina.

Qiu, J., Chen, W., Gao, X., Xu, Y., Tong, H., Yang, M., . . . Yang, M. (2013). A randomized controlled trial of group cognitive behavioral therapy for Chinese breast cancer patients with major depression. *Journal of Psychosomatic Obstetrics and Gynaecology*, *34*(2), 60-67.

Rahman, A., Malik, A., Sikander, S., Roberts, C., & Creed, F. (2008). Cognitive behaviour therapy-based intervention by community health workers for mothers with depression and their infants in rural Pakistan: A cluster-randomised controlled trial. *Lancet*, *372*(9642), 902-909.

Ransom, D., Heckman, T. G., Anderson, T., Garske, J., Holroyd, K., & Basta, T. (2008). Telephone-delivered, interpersonal psychotherapy for HIV-infected rural persons with depression: A pilot trial. *Psychiatric Services*, *59*(8), 871-877.

Rehm, L. P., Kornblith, S. J., O'Hara, M. W., Lamparski, D. M., Romano, J. M., & Volkin, J. I. (1981). An evaluation of major components in a self-control therapy program for depression. *Behavior Modification*, *5*(4), 459-489.

Richards, D., Timulak, L., O'Brien, E., Hayes, C., Vigano, N., Sharry, J., & Doherty, G. (2015). A randomized controlled trial of an internet-delivered treatment: Its potential as a low-intensity community intervention for adults with symptoms of depression. *Behaviour Research and Therapy*, *75*, 20-31.

Rizvi, S. J., Zaretsky, A., Schaffer, A., & Levitt, A. (2015). Is immediate adjunctive CBT more beneficial than delayed CBT in treating depression?: A Pilot Study. *Journal of Psychiatric Practices*, *21*(2), 107-113.

Rohan, K. J., Roecklein, K. A., Lindsey, K. T., Johnson, L. G., Lippy, R. D., Lacy, T. J., & Barton, F. B. (2007). A randomized controlled trial of cognitive-behavioral therapy, light therapy, and their combination for seasonal affective disorder. *Journal of Consulting and Clinical Psychology*, *75*(3), 489-500.

Rohen, N. A. (2002). Analysis of eβcacy and mediators of outcome in minimal-contact cognitive bibliotherapy used in the treatment of depressive symptoms. (doctoral dissertation), University of Alabama.

Rohricht, F., Papadopoulos, N., & Priebe, S. (2013). An exploratory randomized controlled trial of body psychotherapy for patients with chronic depression. *Journal of Affective Disorders*, *151*(1), 85-91.

Ross, M., & Scott, M. (1985). An evaluation of the effectiveness of individual and group cognitive therapy in the treatment of depressed patients in an inner city health centre. The *Journal of the Royal College of General Practitioners*, *35*(274), 239-242.

Rude, S. S. (1986). Relative benefits of assertion or cognitive self-control treatment for depression as a function of proficiency in each domain. *Journal of Consulting and Clinical Psychology*, *54*(3), 390-394.

Ruwaard, J., Schrieken, B., Schrijver, M., Broeksteeg, J., Dekker, J., Vermeulen, H., & Lange, A. (2009). Standardized web-based cognitive behavioural therapy of mild to moderate depression: A randomized controlled trial with a long-term follow-up. *Cognitive Behaviour Therapy*, *38*(4), 206-221.

Safren, S. A., Gonzalez, J. S., Wexler, D. J., Psaros, C., Delahanty, L. M., Blashill, A. J., . . . Cagliero, E. (2014). A randomized controlled trial of cognitive behavioral therapy for adherence and depression (CBT-AD) in patients with uncontrolled type 2 diabetes. *Diabetes Care*, *37*(3), 625-633.

Safren, S. A., O'Cleirigh, C., Tan, J. Y., Raminani, S. R., Reilly, L. C., Otto, M. W., & Mayer, K. H. (2009). A randomized controlled trial of cognitive behavioral therapy for adherence and depression (CBT-AD) in HIV-infected individuals. *Health Psychology*, *28*(1), 1-10.

Savard, J., Simard, S., Giguere, I., Ivers, H., Morin, C. M., Maunsell, E., . . . Marceau, D. (2006). Randomized clinical trial on cognitive therapy for depression in women with metastatic breast cancer: Psychological and immunological effects. *Palliat Support Care*, *4*(3), 219-237.

Schmidt, M. M., & Miller, W. R. (1983). Amount of therapist contact and outcome in a multidimensional depression treatment program. *Acta Psychiatrica Scandinavica*, *67*(5), 319-332.

Schmitt, S. (1988). *Clinical depression: A comparative outcome study of two treatment approaches*. (unpublished doctoral dissertation.), Fairleigh Dickinson University.

Schulberg, H. C., Block, M. R., Madonia, M. J., Scott, C. P., Rodriguez, E., Imber, S. D., . . . Coulehan, J. L. (1996). Treating major depression in primary care practice. Eight-month clinical outcomes. *Archives of General Psychiatry*, *53*(10), 913-919.

Scogin, F., Hamblin, D., & Beutler, L. (1987). Bibliotherapy for depressed older adults: A self-help alternative. *The Gerontologist*, *27*(3), 383-387.

Scogin, F., Jamison, C., & Gochneaur, K. (1989). Comparative efficacy of cognitive and behavioral bibliotherapy for mildly and moderately depressed older adults. *Journal of Consulting and Clinical Psychology*, *57*(3), 403-407.

Scogin, F. R., Moss, K., Harris, G. M., & Presnell, A. H. (2014). Treatment of depressive symptoms in diverse, rural, and vulnerable older adults. *International Journal of Geriatric Psychiatry*, *29*(3), 310-316.

Scott, A. I., & Freeman, C. P. (1992). Edinburgh primary care depression study: Treatment outcome, patient satisfaction, and cost after 16 weeks. *Bmj*, *304*(6831), 883-887.

Scott, C., Tacchi, M. J., Jones, R., & Scott, J. (1997). Acute and one-year outcome of a randomised controlled trial of brief cognitive therapy for major depressive disorder in primary care. *British Journal of Psychiatry*, *171*, 131-134.

Scott, M. J., & Stradling, S. G. (1990). Group cognitive therapy for depression produces clinically significant reliable change in community-based settings. *Behavioural Psychotherapy*, *18*(01), 1-19.

Segre, L. S., Brock, R. L., & O'Hara, M. W. (2015). Depression treatment for impoverished mothers by point-of-care providers: A randomized controlled trial. *Journal of Consulting and Clinical Psychology*, *83*(2), 314-324.

Selmi, P. M., Klein, M. H., Greist, J. H., Sorrell, S. P., & Erdman, H. P. (1990). Computer-administered cognitive-behavioral therapy for depression. *American Journal of Psychiatry*, *147*(1), 51-56.

Serfaty, M. A., Haworth, D., Blanchard, M., Buszewicz, M., Murad, S., & King, M. (2009). Clinical effectiveness of individual cognitive behavioral therapy for depressed older people in primary care: A randomized controlled trial. *Arch Gen Psychiatry*, *66*(12), 1332-1340.

Serrano, J. P., Latorre, J. M., Gatz, M., & Montanes, J. (2004). Life review therapy using autobiographical retrieval practice for older adults with depressive symptomatology. *Psychology and Aging*, *19*(2), 270-277.

Serrano Selva, J. P., Latorre Postigo, J. M., Ros Segura, L., Navarro Bravo, B., Aguilar Corcoles, M. J., Nieto Lopez, M., . . . Gatz, M. (2012). Life review therapy using autobiographical retrieval practice for older adults with clinical depression. *Psicothema*, *24*(2), 224-229.

Shaw, B. F. (1977). Comparison of cognitive therapy and behavior therapy in the treatment of depression. *Journal of Consulting and Clinical Psychology*, *45*(4), 543.

Sheeber, L. B., Seeley, J. R., Feil, E. G., Davis, B., Sorensen, E., Kosty, D. B., & Lewinsohn, P. M. (2012). Development and pilot evaluation of an Internet-facilitated cognitive-behavioral intervention for maternal depression. *Journal of Consulting and Clinical Psychology*, *80*(5), 739-749.

Simpson, S., Corney, R., Fitzgerald, P., & Beecham, J. (2000). A randomised controlled trial to evaluate the effectiveness and cost-effectiveness of counselling patients with chronic depression. *Health Technology Assessment*, *4*(36), 1-83.

Simson, U., Nawarotzky, U., Friese, G., Porck, W., Schottenfeld-Naor, Y., Hahn, S., . . . Kruse, J. (2008). Psychotherapy intervention to reduce depressive symptoms in patients with diabetic foot syndrome. *Diabetic Medicine*, *25*(2), 206-212.

Skinner, D. (1983). *Self-control of depression: A comparison of behavior therapy and cognitive behavior therapy.* (unpublished doctoral dissertation.), United States International University.

Sloane, R., Staples, F., & Schneider, L. (1985). Interpersonal therapy versus nortriptyline for depression in the elderly. *Clinical and Pharmacological Studies in Psychiatric Disorders*, 344-346.

Smit, A., Kluiter, H., Conradi, H. J., Meer, K., Tiemens, B. G., Jenner, J. A., . . . Ormel, J. (2006). Short-term effects of enhanced treatment for depression in primary care: results from a randomized controlled trial. *Psychological Medicine*, *36*(1), 15-26.

Songprakun, W., & McCann, T. V. (2012). Evaluation of a cognitive behavioural self-help manual for reducing depression: A randomized controlled trial. *Journal of Psychiatric Mental Health Nursing*, *19*(7), 647-653.

Spek, V., Nyklicek, I., Smits, N., Cuijpers, P., Riper, H., Keyzer, J., & Pop, V. (2007). Internet-based cognitive behavioural therapy for subthreshold depression in people over 50 years old: A randomized controlled clinical trial. *Psychological Medicine*, *37*(12), 1797-1806.

Spinelli, M. G., & Endicott, J. (2003). Controlled clinical trial of interpersonal psychotherapy versus parenting education program for depressed pregnant women. *American Journal of Psychiatry*, *160*(3), 555-562.

Spinelli, M. G., Endicott, J., Leon, A. C., Goetz, R. R., Kalish, R. B., Brustman, L. E., . . . Schulick, J. L. (2013). A controlled clinical treatment trial of interpersonal psychotherapy for depressed pregnant women at 3 New York City sites. *Journal of Clinical Psychiatry*, *74*(4), 393-399.

Sreevani, R., Reddemma, K., Chan, C. L., Leung, P. P., Wong, V., & Chan, C. H. (2013). Effectiveness of integrated body-mind-spirit group intervention on the well-being of Indian patients with depression: A pilot study. *Journal of Nursing Research*, *21*(3), 179-186.

Strauss, C., Hayward, M., & Chadwick, P. (2012). Group person-based cognitive therapy for chronic depression: A pilot randomized controlled trial. *British Journal of Clinical Psychology*, *51*(3), 345-350.

Strong, V., Waters, R., Hibberd, C., Murray, G., Wall, L., Walker, J., . . . Sharpe, M. (2008). Management of depression for people with cancer (SMaRT oncology 1): A randomised trial. *Lancet*, *372*(9632), 40-48.

Sudweeks, C. (1996). Effects of cognitive group hypnotherapy in the alteration of depressogenic schemas. (doctoral dissertation), Washington State University.

Swartz, H. A., Frank, E., Zuckoff, A., Cyranowski, J. M., Houck, P. R., Cheng, Y., . . . Shear, M. K. (2008). Brief interpersonal psychotherapy for depressed mothers whose children are receiving psychiatric treatment. *American Journal of Psychiatry*, *165*(9), 1155-1162.

Talbot, N. L., Chaudron, L. H., Ward, E. A., Duberstein, P. R., Conwell, Y., O'Hara, M. W., . . . Stuart, S. (2011). A randomized effectiveness trial of interpersonal psychotherapy for depressed women with sexual abuse histories. *Psychiatric Services*, *62*(4), 374-380.

Taylor, C. B., Conrad, A., Wilhelm, F. H., Strachowski, D., Khaylis, A., Neri, E., . . . Spiegel, D. (2009). Does improving mood in depressed patients alter factors that may affect cardiovascular disease risk? *Journal of Psychiatric Research*, *43*(16), 1246-1252.

Taylor, F. G., & Marshall, W. L. (1977). Experimental analysis of a cognitive-behavioral therapy for depression. *Cognitive Therapy and Research*, *1*(1), 59-72.

Teasdale, J. D., Fennell, M. J., Hibbert, G. A., & Amies, P. L. (1984). Cognitive therapy for major depressive disorder in primary care. *British Journal of Psychiatry*, *144*, 400-406.

Teichman, Y., Bar-el, Z., Shor, H., Sirota, P., & Elizur, A. (1995). A comparison of two modalities of cognitive therapy (individual and marital) in treating depression. *Psychiatry*, *58*(2), 136-148.

Teri, L., Logsdon, R. G., Uomoto, J., & McCurry, S. M. (1997). Behavioral treatment of depression in dementia patients: A controlled clinical trial. *Journal of Gerontology series B: Psychological Sciences and Social Sciences*, *52*(4), P159-166.

Titov, N., Andrews, G., Davies, M., McIntyre, K., Robinson, E., & Solley, K. (2010). Internet treatment for depression: A randomized controlled trial comparing clinician vs. technician assistance. *PLoS ONE*, *5*(6), e10939.

Titov, N., Dear, B. F., Ali, S., Zou, J. B., Lorian, C. N., Johnston, L., . . . Fogliati, V. J. (2015). Clinical and cost-effectiveness of therapist-guided internet-delivered cognitive behavior therapy for older adults with symptoms of depression: A randomized controlled trial. *Behav Ther*, *46*(2), 193-205.

Tovote, K. A., Fleer, J., Snippe, E., Peeters, A., Emmelkamp, P. M. G., Sanderman, R., . . . Schroevers, M. J. (2014). Individual mindfulness-based cognitive therapy and cognitive behavior therapy for treating depressive symptoms in patients with diabetes: Results of a randomized controlled trial. *Diabetes Care*, *37*(9), 2427-2434.

Turner, A., Hambridge, J., Baker, A., Bowman, J., & McElduff, P. (2013). Randomised controlled trial of group cognitive behaviour therapy versus brief intervention for depression in cardiac patients. *Australian and New Zealand Journal of Psychiatry*, *47*(3), 235-243.

Turner, R. W., Ward, M. F., & Turner, D. J. (1979). Behavioral treatment for depression: An evaluation of therapeutic components. *Journal of Clinical Psychology*, *35*(1), 166-175.

Tyson, G. M., & Range, L. M. (1987). Gestalt dialogues as a treatment for mild depression: Time works just as well. *Journal of Clinical Psychology*, *43*(2), 227-231.

Unlu Ince, B., Cuijpers, P., t Hof, E., Ballegooijen, W., Christensen, H., & Riper, H. (2013). Internet-based, culturally sensitive, problem-solving therapy for Turkish migrants with depression: Randomized controlled trial. *Journal of Medical Internet Research*, *15*(10), e227.

van Bastelaar, K. M., Pouwer, F., Cuijpers, P., Riper, H., & Snoek, F. J. (2011). Web-based depression treatment for type 1 and type 2 diabetic patients: A randomized, controlled trial. *Diabetes Care*, *34*(2), 320-325.

van Schaik, A., van Marwijk, H., Adèr, H., van Dyck, R., de Haan, M., Penninx, B., . . . Beekman, A. (2006). Interpersonal psychotherapy for elderly patients in primary care. *The American Journal of Geriatric Psychiatry*, *14*(9), 777-786.

Verduyn, C., Barrowclough, C., Roberts, J., Tarrier, N., & Harrington, R. (2003). Maternal depression and child behaviour problems: Randomised placebo-controlled trial of a cognitive-behavioural group intervention. *British Journal of Psychiatry*, *183*(4), 342-348.

Vernmark, K., Lenndin, J., Bjärehed, J., Carlsson, M., Karlsson, J., Oberg, J., . . . Andersson, G. (2010). Internet administered guided self-help versus individualized e-mail therapy: A randomized trial of two versions of CBT for major depression. *Behaviour Research and Therapy*, *48*(5), 368-376.

Vitriol, V. G., Ballesteros, S. T., Florenzano, R. U., Weil, K. P., & Benadof, D. F. (2009). Evaluation of an outpatient intervention for women with severe depression and a history of childhood trauma. *Psychiatric Services*, *60*(7), 936-942.

Warmerdam, L., Straten, A., Twisk, J., Riper, H., & Cuijpers, P. (2008). Internet-based treatment for adults with depressive symptoms: Randomized controlled trial. *Journal of Medical Internet Research*, *10*(4), e44.

Watkins, E. R., Baeyens, C. B., & Read, R. (2009). Concreteness training reduces dysphoria: Proof-of-principle for repeated cognitive bias modification in depression. *Journal of Abnormal Psychology*, *118*(1), 55-64.

Watkins, E. R., Taylor, R. S., Byng, R., Baeyens, C., Read, R., Pearson, K., & Watson, L. (2012). Guided self-help concreteness training as an intervention for major depression in primary care: A phase II randomized controlled trial. *Psychological Medicine*, *42*(7), 1359-1371.

Watt, L. M., & Cappeliez, P. (2000). Integrative and instrumental reminiscence therapies for depression in older adults: Intervention strategies and treatment effectiveness. *Aging and Mental Health*, *4*(2), 166-177.

Weissman, M. M., Prusoff, B. A., Dimascio, A., Neu, C., Goklaney, M., & Klerman, G. L. (1979). The efficacy of drugs and psychotherapy in the treatment of acute depressive episodes. *American Journal of Psychiatry*, *136*(4b), 555-558.

Wickberg, B., & Hwang, C. P. (1996). Counselling of postnatal depression: A controlled study on a population based Swedish sample. *Journal of Affective Disorders*, *39*(3), 209-216.

Wiklund, I., Mohlkert, P., & Edman, G. (2010). Evaluation of a brief cognitive intervention in patients with signs of postnatal depression: A randomized controlled trial. *Acta Obstet Gynecol Scand*, *89*(8), 1100-1104.

Williams, J. W., Barrett, J., Oxman, T., Frank, E., Katon, W., Sullivan, M., . . . Sengupta, A. (2000). Treatment of dysthymia and minor depression in primary care: A randomized controlled trial in older adults. *Jama*, *284*(12), 1519-1526.

Wilson, P. H., Goldin, J. C., & Charbonneau-Powis, M. (1983). Comparative efficacy of behavioral and cognitive treatments of depression. *Cognitive Therapy and Research*, *7*(2), 111-124.

Wollersheim, J. P., & Wilson, G. L. (1991). Group treatment of unipolar depression: A comparison of coping, supportive, bibliotherapy, and delayed treatment groups. *Professional Psychology: Research and Practice*, *22*(6), 496.

Wong, D. F. (2008a). Cognitive and health-related outcomes of group cognitive behavioural treatment for people with depressive symptoms in Hong Kong: Randomized wait-list control study. *Australian and New Zealand Journal of Psychiatry*, *42*(8), 702-711.

Wong, D. F. (2008b). Cognitive behavioral treatment groups for people with chronic depression in Hong Kong: A randomized wait-list control design. *Depression and Anxiety*, *25*(2), 142-148.

Wright, J. H., Wright, A. S., Albano, A. M., Basco, M. R., Goldsmith, L. J., Raffield, T., & Otto, M. W. (2005). Computer-assisted cognitive therapy for depression: Maintaining efficacy while reducing therapist time. *American Journal of Psychiatry*, *162*(6), 1158-1164.

Wuthrich, V. M., & Rapee, R. M. (2013). Randomised controlled trial of group cognitive behavioural therapy for comorbid anxiety and depression in older adults. *Behaviour Research and Therapy*, *51*(12), 779-786.

Zu, S., Xiang, Y.-T., Liu, J., Zhang, L., Wang, G., Ma, X., . . . Li, Z.-J. (2014). A comparison of cognitive-behavioral therapy, antidepressants, their combination and standard treatment for Chinese patients with moderate–severe major depressive disorders. *Journal of Affective Disorders*, *152-154*, 262

APPENDIX E (CHAPTER 6)

E1. TABLES

Table a. Studies Characteristics

Studies	Diagnosis	Recruitment	N sessions	Intervention	N –intervention	Control group	N - Control	Outcome measure	IPD available	Average no of sessions completed	Country
Berger et al. (2011)	BDI-II > 13	Community	11	F-SG CBT	25	WL	26	BDI-II	Yes	7	CH
Christensen et al. (2004)	K10 > 21	Community	5	TS - CBT	182	Attention placebo	178	CESD	Yes	NR	AU
Clarke et al. (2002)	Depression (HMO diagnosis)	HMO	7	F-SG CBT	144	TAU	155	CESD	No	NA	US
Clarke et al. (2005)	Depression (HMO diagnosis)	HMO	7	TS CBT	155	TAU	100	CESD	No	NA	US
Clarke et al. (2009)	Depression (HMO diagnosis)	HMO	7	F-SG CBT	83	TAU	77	PHQ-8	No	NA	US
De Graaf et al. (2009)	BDI-II > 15	Primary care	9	F-SG CBT CBT&TAU	100 100	TAU	100	BDI-II	Yes	4	NL
Farrer et al. (2011)	K10 > 22	Tel-counselling service	5	F-SG CBT TS CBT	38 45	No treatment	35	CESD	Yes	2	AU
Gilbody et al. (2015)	PHQ-9 > 9	Primary care	8 5	TS CBT gr1[a] TS CBT gr2[a]	210 242	TAU	239	PHQ-9	Yes	2	UK
Kleiboer et al. (2015)	CESD > 15 CESD < 40	Community	5	F-SG CBT	107	WL	106	CESD	Yes	2	NL
Klein et al. (2016)	PHQ-9 > 4; PHQ-9 < 15	Community & primary care	11	F-SG CBT	192	TAU	187	PHQ-9	Yes	NR	DE
Meyer et al. (2009)	Depression (BDI)	Community	11	F-SG CBT	320	WL	76	BDI	Yes	4	DE

continued

Table a. Studies Characteristics (continued)

Studies	Diagnosis	Recruitment	N sessions	Intervention	N –intervention	Control group	N - Control	Outcome measure	IPD available	Average no of sessions completed	Country
Meyer et al. (2015)	PHQ-9 > 14	Community & primary care	11	F-SG CBT	78	TAU	85	PHQ-9	Yes	8	DE
Mira et al. (submitted)	Mild to moderate depression (BDI < 28)	Community	8	TS - CBT	44	WL	44	BDI-II	Yes	7	SP
Moritz et al. (2012)	Depression (BDI)	Community	11	F-SG CBT	105	WL	105	BDI	Yes	6	DE
Phillips et al. (2014)	PHQ-9 > 9	Workplaces	5	F-SG CBT	318	Attention placebo	319	PHQ-9	Yes	NR	UK
Spek et al. (2007)	EDS > 12	Community	10	F-SG CBT	67	WL	58	BDI	Yes	5	NL

&TAU: Self-guided web based CBT combined with TAU; AU: Australia; BDI: Beck Depression Inventory; CESD: Centre of Epidemiological Studies Depression Scale; CH: Switzerland; DE: Germany; EDS: The Edinburgh Depression Scale; F-SG: Full self-guided; gr: group; HMO: non-profit Health Maintenance Origination; K10: Kessler Psychological Distress Scale; N: Number of participants; NA: Not available' NL: the Netherlands; no: number; NR: Not reported; PHQ: Patient Health Questionnaire; SP: Spain; TAU: Treatment As Usual; TS: support for technical issues related to the website usage; UK: the United kingdom; US: the United States; WL: Waiting List

[a] Both Group 1 and Group 2 were forms of web-based CBT for which technical support only was available, used as an adjunct to treatment as usual

[b] Klein et al. 2016 trial provided therapeutic support to participants with moderate symptoms of depression at the baseline (PHQ-9 > 9) while participants with mild depressive symptoms received no support throughout the trial. Participants of this trial were stratified by severity of depression during randomization and thus, we decided to exclude all participants who received therapeutic support (PHQ-9 > 9; n = 634) from all the analyses of the present IPD meta-analysis.

Table b. Demographic and clinical characteristics of the included sample

Characteristics	
Mean Age in years (SD)	42 (11.7)
Gender, females, n (%)	2531/3832 (66)
Education, secondary education, n (%)	1368/2574 (53)
Employed, n (%)	2262/3146 (72)
Being in a relationship, n (%)	2119/3613(59)
Participants who did not provide BL data, n (%)	71/3876 (1.8)
Participants who dropped out from studies, n (%)	1048/3876 (27)
CES-D at the baseline, mean (SD)	25.7 (10.8)
BDI at the baseline, mean (SD)	28.3 (14.4)
PHQ-9 at the baseline, mean (SD)	14.1 (5.4)
Comorbid Anxiety, n (%)	761/1761 (43)

BDI: Beck Depression Inventory; CES-D: Centre of Epidemiological studies for depression scale; n: number of patients; PHQ-9: the Patient Health Questionnaire – 9 items; SD: Standard Deviation

Table c. Risk of bias assessment

Study: Berger, Hammerli, Gubser, Andersson, and Caspar (2011)		
Bias	**Authors' judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk of bias	*'Participants were randomized into one of the three conditions using a computerized random number generator'* (www.random.org) (p. 257)(Berger et al., 2011)
Allocation concealment (selection bias)	Low risk of bias	*'The allocation schedule was generated by an independent researcher'* (p. 257) (Berger et al., 2011)
Blinding of participants and personnel (performance bias)	Not applicable	Blinding of participants and personnel is not possible in psychotherapy research due to the nature of the treatment.
Blinding of outcome assessment (detection bias)	Not applicable	Use of self-report outcome measures.
Incomplete outcome data (attrition bias)	Low risk of bias	Missing values were imputed by the IPD meta-analysis (see IPD meta-analysis methods section).
Selective reporting (reporting bias)	Low risk of bias	The study protocol is not available but it is clear that the published report includes all expected outcomes, including those that were pre-specified.
Other bias	Low risk of bias	The study appears to be free of other sources of bias.
Study: Christensen, Griffiths, and Jorm (2004)		
Bias	**Authors' judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk of bias	According to the authors, computer-generated random numbers (using SPSS) were used to assign participants to treatment arms.
Allocation concealment (selection bias)	Low risk of bias	According to the authors, an independent statistician performed the randomization and the allocation was concealed from the investigators.
Blinding of participants and personnel (performance bias)	Not applicable	Blinding of participants and personnel is not possible in psychotherapy research due to the nature of the treatment.
Blinding of outcome assessment (detection bias)	Not applicable	Use of self-report outcome measures.
Incomplete outcome data (attrition bias)	Low risk of bias	Missing values were imputed by the IPD meta-analysis (see IPD meta-analysis methods section).
Selective reporting (reporting bias)	Low risk of bias	No indication of selective reporting based on the trial registration (ISRCTN77824516).
Other bias	Low risk of bias	The study appears to be free of other sources of bias.

continued

Table c. Risk of bias assessment (continued)

Study: De Graaf et al. 2009		
Bias	**Authors' judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk of bias	*'The randomization code will be given to an independent IT-specialist who will develop a computer program to carry out the group allocation. On entry into the trial the computer program provides the next available number.'* (p. 4 of the protocol de Graaf et al. 2008)(de Graaf et al., 2008)
Allocation concealment (selection bias)	Low risk of bias	*'The randomization code will not be revealed until participant inclusion is complete.'* (p. 4 of the protocol de Graaf et al. 2008)(de Graaf et al., 2008)
Blinding of participants and personnel (performance bias)	Not applicable	Blinding of participants and personnel is not possible in psychotherapy research due to the nature of the treatment.
Blinding of outcome assessment (detection bias)	Not applicable	Use of self-report outcome measures.
Incomplete outcome data (attrition bias)	Low risk of bias	Missing values were imputed by the IPD meta-analysis (see IPD meta-analysis methods section).
Selective reporting (reporting bias)	Low risk of bias	No indication of selective reporting based on the published protocol (de Graaf et al. 2008)(de Graaf et al., 2008)
Other bias	Low risk of bias	The study appears to be free of other sources of bias.
Study: Farrer, Christensen, Griffiths, and Mackinnon (2011)		
Bias	**Authors' judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk of bias	*'A block randomization procedure with stratification based on sex, site of recruitment and severity of psychological distress at screening was used.'* (p. e28099)(Farrer et al., 2011)
Allocation concealment (selection bias)	Low risk of bias	*'Allocation of participants to trial conditions was conducted independently by a research assistant not otherwise involved with the trial'* (p. e28099)(Farrer et al., 2011)
Blinding of participants and personnel (performance bias)	Not applicable	Blinding of participants and personnel is not possible in psychotherapy research due to the nature of the treatment.
Blinding of outcome assessment (detection bias)	Not applicable	Use of self-report outcome measures.
Incomplete outcome data (attrition bias)	Low risk of bias	Missing values were imputed by the IPD meta-analysis (see IPD meta-analysis methods section).
Selective reporting (reporting bias)	Low risk of bias	No indication of selective reporting based on the trial registration (ISRCTN93903959).
Other bias	Low risk of bias	The study appears to be free of other sources of bias.

continued

Table c. Risk of bias assessment (continued)

Study: Gilbody et al. (2015)		
Bias	**Authors' judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk of bias	*'Participants were allocated by simple randomization to one of three groups without any restrictions placed on the sequence (that is, no blocking or stratification was included in the randomization procedure)'* (page 3)(Gilbody et al., 2015)
Allocation concealment (selection bias)	Low risk of bias	*'At the point of recruitment we used an automated computer data entry system to conceal treatment allocation from the study researchers. This was administered remotely by the York Trials Unit and used a computer-generated code'* (page 3)(Gilbody et al., 2015)
Blinding of participants and personnel (performance bias)	Not applicable	Blinding of participants and personnel is not possible in psychotherapy research due to the nature of the treatment.
Blinding of outcome assessment (detection bias)	Not applicable	Use of self-report outcome measures.
Incomplete outcome data (attrition bias)	Low Risk of bias	Missing values were imputed by the IPD meta-analysis (see IPD meta-analysis methods section).
Selective reporting (reporting bias)	Low risk of bias	No indication of selective reporting based on the trial registration (ISRCTN91947481).
Other bias	Low risk of bias	The study appears to be free of other sources of bias.
Study: Kleiboer et al. (2015)		
Bias	**Authors' judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk of bias	*'Random allocation took place at the individual level by an independent researcher who was not involved in the study. The allocation schedule was derived by computer using a random number generator. Block randomization was applied with variable block sizes containing 6, 8, 10, or 12 allocations'* (p. 64)(Kleiboer et al., 2015)
Allocation concealment (selection bias)	Low risk of bias	*'The allocation schedule will be made with a computerized random number generator by an independent researcher and will be unknown to the investigators.'* (From protocol Donker et al. 2009 p. 3)(Donker et al., 2009)
Blinding of participants and personnel (performance bias)	Not applicable	Blinding of participants and personnel is not possible in psychotherapy research due to the nature of the treatment.
Blinding of outcome assessment (detection bias)	Not applicable	Use of self-report outcome measures
Incomplete outcome data (attrition bias)	Low Risk of bias	Missing values were imputed by the IPD meta-analysis (see IPD meta-analysis methods section).
Selective reporting (reporting bias)	Low Risk of bias	No indication of selective reporting based on the published protocol (Donker et al. 2009)(Donker et al., 2009)
Other bias	Low Risk of bias	The study appears to be free of other sources of bias.

continued

Table c. Risk of bias assessment (continued)

Study: Klein et al. 2016		
Bias	**Authors' judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk of bias	*'Participants were randomized equally (1:1) to the two groups (intervention or control). Randomization was stratified by the PHQ-9 (PHQ-9 <10 vs. PHQ-9 ≥10). Block randomization with variable block sizes was used.'* (p. 220)(Jan Philipp Klein et al., 2016)
Allocation concealment (selection bias)	Low risk of bias	*'The allocation schedule was created by an independent investigator with a computerized random number generator; the other investigators were blinded to this schedule'* (p. 220)(Jan Philipp Klein et al., 2016)
Blinding of participants and personnel (performance bias)	Not applicable	Blinding of participants and personnel is not possible in psychotherapy research due to the nature of the treatment.
Blinding of outcome assessment (detection bias)	Not applicable	Use of self-report outcome measures.
Incomplete outcome data (attrition bias)	Low Risk of bias	Missing values were imputed by the IPD meta-analysis (see IPD meta-analysis methods section)
Selective reporting (reporting bias)	Low Risk of bias	No indication of selective reporting based on the published protocol (Klein et al. 2013)(Jan P Klein et al., 2013)
Other bias	Low Risk of bias	The study appears to be free of other sources of bias.
Study: Meyer et al. 2009		
Bias	**Authors' judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk of bias	*'Randomization was performed via a computer-generated list of random numbers. After generating a list of 500 random numbers and sorting them by size, the highest 20% were marked to indicate that they referred to the control condition. The list was then resorted to its original order and newly enrolled participants were consecutively placed onto this list. If a new participant received a marked number, he or she was assigned to the control condition; otherwise, the new participant was assigned to the immediate-access condition. This procedure ensured that an 80:20 chance—but no predictable sequence—existed with regard to whether a new participant would be assigned to the immediate-access or the delayed-access condition'* (p.5)(B. Meyer et al., 2009)

continued

Table c. Risk of bias assessment (continued)

Study: Meyer et al. 2009		
Bias	**Authors' judgment**	**Support for judgment**
Allocation concealment (selection bias)	Low risk of bias	According to the authors: The way they concealed allocation, is as follows: * A research assistant checked whether all inclusion and exclusion criteria were met, so that the person could be admitted to the trial and randomized. * If criteria were met and the person was admitted, this research assistant informed the Principal Investigator and/or the person who was the study/project manager that this particular person had been included and is "ready for randomization". All that was given was the participant ID but no other information, such as any participant data. * The PI and/or project study manager then placed the included participant's ID on the pre-generated list of random numbers. This list was not known or available to the research assistant because it was kept in an encrypted, password-protected file to which only the PI and/or study manager had access. * The PI and/or study manager then performed the randomization by placing the ID onto this list, and then they informed the research assistant about the randomization result. * After this, the research assistant could proceed to inform the participant about the randomization result and provided further instructions regarding next steps. This method is an adequate way of achieving concealed allocation because there is no way that the person responsible for admitting participants into the trial can know what the upcoming group assignment will be.
Blinding of participants and personnel (performance bias)	Not applicable	Blinding of participants and personnel is not possible in psychotherapy research due to the nature of the treatment.
Blinding of outcome assessment (detection bias)	Not applicable	Use of self-report outcome measures.
Incomplete outcome data (attrition bias)	Low Risk of bias	Missing values were imputed by the IPD meta-analysis (see IPD meta-analysis methods section).
Selective reporting (reporting bias)	Low risk of bias	No indication of selective reporting based on the trial registration (ISRCTN64953693/64953693).
Other bias	Low risk of bias	The study appears to be free of other sources of bias.

continued

Table c. Risk of bias assessment (continued)

Study: Meyer et al. 2015		
Bias	**Authors' judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low Risk of bias	*'Randomization was conducted with an allocation schedule of random numbers that was created by a computerized random number generator'* (p. 50)(Björn Meyer et al., 2015)
Allocation concealment (selection bias)	Low Risk of bias	*'Participants who were deemed eligible after the telephone interview were consecutively placed on this list by one of the researchers (J.B.), who did not conduct telephone interviews and did not have contact with or knowledge of individual study participants'* (p. 50)(Björn Meyer et al., 2015)
Blinding of participants and personnel (performance bias)	Not applicable	Blinding of participants and personnel is not possible in psychotherapy research due to the nature of the treatment.
Blinding of outcome assessment (detection bias)	Not applicable	Use of self-report outcome measures.
Incomplete outcome data (attrition bias)	Low Risk of bias	Missing values were imputed by the IPD meta-analysis (see IPD meta-analysis methods section).
Selective reporting (reporting bias)	Low risk of bias	No indication of selective reporting based on trial registration (NCT02178631).
Other bias	Low risk of bias	The study appears to be free of other sources of bias.
Study: Mira et al. (submitted)		
Bias	**Authors' judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk of bias	According to the authors, the random sequence was generated by the computer software Random Allocation, version 1.0. Participants were stratified based on depression severity.
Allocation concealment (selection bias)	Low risk of bias	According to the authors, an independent researcher performed the randomization and the allocation was concealed from the investigators.
Blinding of participants and personnel (performance bias)	Not applicable	Blinding of participants and personnel is not possible in psychotherapy research due to the nature of the treatment.
Blinding of outcome assessment (detection bias)	Not applicable	Use of self-report outcome measures.
Incomplete outcome data (attrition bias)	Low Risk of bias	Missing values were imputed by the IPD meta-analysis (see IPD meta-analysis methods section).
Selective reporting (reporting bias)	Low Risk of bias	No indication of selective reporting based on the trial registration (NCT02148354).
Other bias	Low Risk of bias	The study appears to be free of other sources of bias.

continued

Table c. Risk of bias assessment (continued)

Study: Moritz, Schilling, Hauschildt, Schroder, and Treszl (2012)		
Bias	**Authors' judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk of bias	According to the authors, a pseudo-random sequence was used.
Allocation concealment (selection bias)	Low risk of bias	According to the authors, allocation was conducted by an independent researcher and it was concealed from the investigators.
Blinding of participants and personnel (performance bias)	Not applicable	Blinding of participants and personnel is not possible in psychotherapy research due to the nature of the treatment.
Blinding of outcome assessment (detection bias)	Not applicable	Use of self-report outcome measures.
Incomplete outcome data (attrition bias)	Low Risk of bias	Missing values were imputed by the IPD meta-analysis (see IPD meta-analysis methods section).
Selective reporting (reporting bias)	Low Risk of bias	No indication of selective reporting based on the trial registration (NCT01401296).
Other bias	Low Risk of bias	The study appears to be free of other sources of bias.
Study: Phillips et al. (2014)		
Bias	**Authors' judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low Risk of bias	*'A list was produced by the Nottingham Clinical Trials Unit to allow simple (unrestricted) randomization'* (p. 743)(Phillips et al., 2014)
Allocation concealment (selection bias)	Low Risk of bias	*'Once potential participants had completed the screening questions, if eligible for inclusion in the trial, they were given a study ID, allocated through the website, and they were then invited to join the trial. If participants consented, they were randomized by the portal designers at ANU. In this way the randomization status of participants was concealed from their employers and from the research team until the study was completed.'* (p.743)(Phillips et al., 2014)
Blinding of participants and personnel (performance bias)	Not applicable	Blinding of participants and personnel is not possible in psychotherapy research due to the nature of the treatment.
Blinding of outcome assessment (detection bias)	Not applicable	Use of self-report outcome measures.
Incomplete outcome data (attrition bias)	Low Risk of bias	Missing values were imputed by the IPD meta-analysis (see IPD meta-analysis methods section)
Selective reporting (reporting bias)	Low Risk of bias	No indication of selective reporting based on the trial registration (ISRCTN24529487).
Other bias	Low Risk of bias	The study appears to be free of other sources of bias.

continued

Table c. Risk of bias assessment (continued)

Study: Spek et al. (2007)		
Bias	**Authors' judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low Risk of bias	According to the authors, a computer random sequence generator was used.
Allocation concealment (selection bias)	Low Risk of bias	*'At the end of the clinical interview, eligible participants were randomized. For this purpose a random allocation sequence was generated. The randomization list was kept in an administrative office that was not related to the study. After the inclusion of a participant in the study, the interviewer made a telephone call to the ' randomization office ' to inquire to which condition the participant was randomized. On the randomization list, the time and date of randomization were noted.'* (p.4)(Spek et al., 2007)
Blinding of participants and personnel (performance bias)	Not applicable	Blinding of participants and personnel is not possible in psychotherapy research due to the nature of the treatment.
Blinding of outcome assessment (detection bias)	Not applicable	Use of self-report outcome measures.
Incomplete outcome data (attrition bias)	Low Risk of bias	Missing values were imputed by the IPD meta-analysis (see IPD meta-analysis methods section).
Selective reporting (reporting bias)	Low Risk of bias	The study protocol is not available but it is clear that the published report includes all expected outcomes, including those that were pre-specified.
Other bias	Low Risk of bias	The study appears to be free of other sources of bias.

Table d. Effect sizes for self-guided iCBT vs. control comparator conditions in adults with depressive symptoms, 2-stage IPD

Outcomes	N	g	95% CI[b]	I^2	95%CI	p[c]
Depression severity at post-treatment full sample	13	0.27	0.17 to 0.37	55%	16 to 76%	<.001
Subgroups						
Type of control						
TAU vs.	4	0.20	-0.02 to 0.42	75%	30 to 91%	.41
Other	9	0.30	0.19 to 0.41	28%	0 to 67%	
Recruitment						
Community	7	0.32	0.22 to 0.43	0%	0 to 71%	
Community and/or primary care	4	0.20	-0.02 to 0.42	75%	30 to 91%	0.60
Other	2	0.34	-0.15 to 0.84	81%	N/A	
Support						
Pure self-guided iCBT	9	0.26	0.16 to 0.36	24%	0 to 64%	.80
Technically supported iCBT	4	0.30	0.02 to 0.59	80%	47 to 92%	
Depression severity at post-treatment Completer sample	13	0.32	0.17 to 0.46	71%	49 to 83%	<.001
Subgroups						
Type of control						
TAU vs.	4	0.20	-0.09 to 0.50	83	58 to 93%	.31
Other	9	0.37	0.22 to 0.52	50%	0 to 77%	
Recruitment						
Community	7	0.40	0.27 to 0.51	0%	0 to 71%	
Community and/or primary care	4	0.20	-0.09 to 0.50	83%	58 to 93%	.50
Other	2	0.37	-0.32 to 1.06	85%	N/A	
Support						
Pure self-guided iCBT	9	0.33	0.18 to 0.47	55%	5 to 79%	.94
Technically supported iCBT	4	0.31	-0.06 to 0.67	85%	62 to 94%	

[a] Subgroup analyses were conducted only in the cases where at least three comparisons were available per group. g = Hedges's g; N: Number of studies; N/A: Not applicable

[b] 95% CI: 95% Confidence Intervals; p: p-value

[c] p-value between groups

Table e. Effect sizes for self-guided iCBT vs. control comparator conditions in adults with depressive symptoms, 2-stage IPD

Outcomes	N	OR	95% CI[b]	I^2	95%CI	p[c]
Treatment response at post-treatment full sample	13	1.95	1.52 to 2.50	52%	9 to 74%	<.001
Subgroups						
Type of control						
TAU vs.	4	1.66	1.05 to 2.63	70%	14 to 90%	.37
Other	9	2.12	1.60 to 2.83	33%	0 to 69%	
Recruitment						
Community	7	2.32	1.36 to 3.06	0%	0 to 71%	
Community and/or primary care	4	1.66	1.05 to 2.62	70%	14 to 90%	.46
Other	2	1.90	0.74 to 4.87	63%	N/A	
Support						
Pure self-guided iCBT	9	2.04	1.52 to 2.74	44%	0 to 74%	.68
Technically supported iCBT	4	1.81	1.09 to 3.01	65%	0 to 88%	
Treatment response at post-treatment Completer sample	13	1.88	1.34 to 2.64	64%	35 to 80%	<.001
Subgroups						
Type of control						
TAU vs.	4	1.63	0.95 to 2.79	74%	27 to 91%	.46
Other	9	2.13	1.31 to 3.42	61%	20 to 81%	
Recruitment						
Community	7	2.22	1.61 to 3.08	3%	0 to 72%	
Community and/or primary care	4	1.63	0.95 to 2.80	74%	27 to 91%	.62
Other	2	1.88	0.27 to 12.75	82%	N/A	
Support						
Pure self-guided iCBT	9	1.97	1.27 to 3.06	64%	26 to 82%	.83
Technically supported iCBT	4	1.82	0.97 to 3.40	71%	17 to 90%	

[a] Subgroup analyses were conducted only in the cases where at least three comparisons were available per group. N: Number of studies

[b] 95% CI: 95% Confidence Intervals; OR: Odds Ratio; p: p-value

[c] p-value between groups

E2 . FIGURES

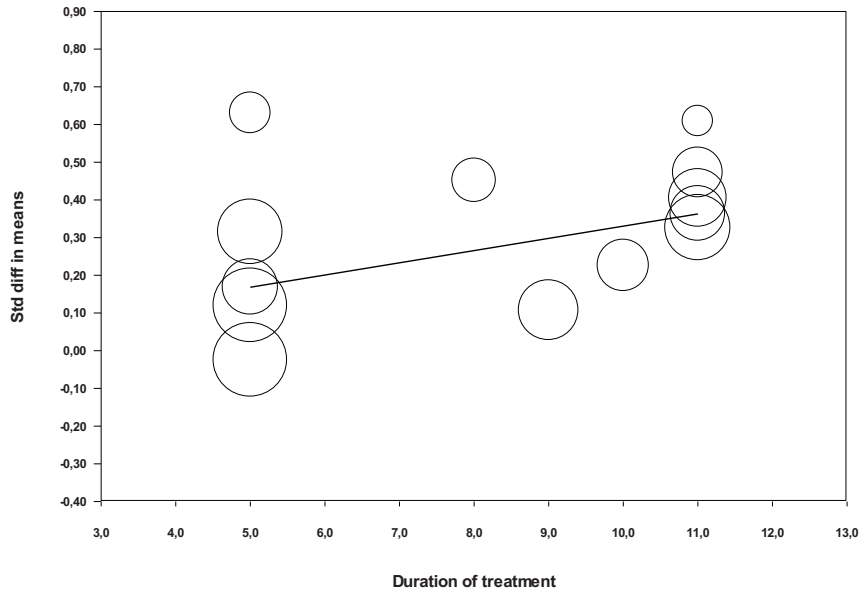


Figure a. Meta-regression of analysis of the association between treatment duration and depression symptoms severity (Full sample)

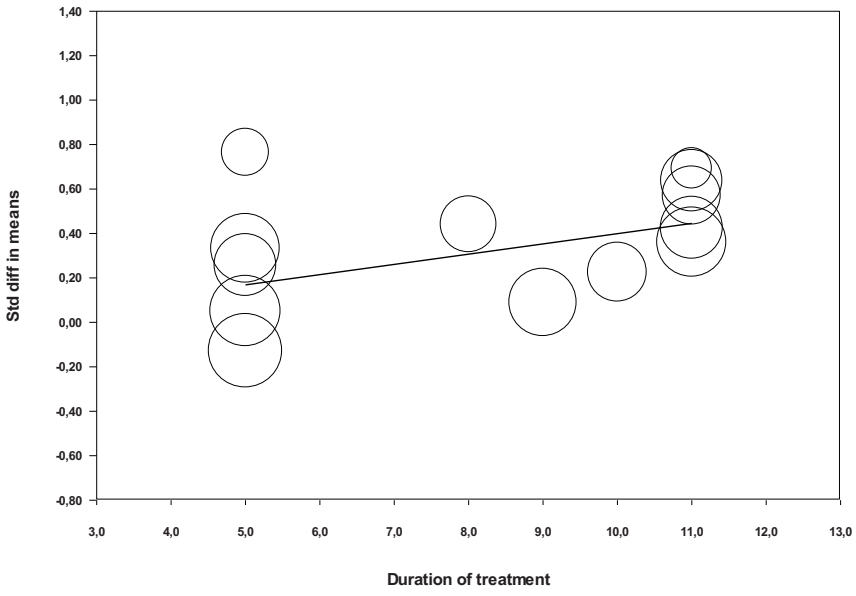


Figure b. Meta-regression of analysis of the association between treatment duration and depression symptoms severity (complete cases sample)

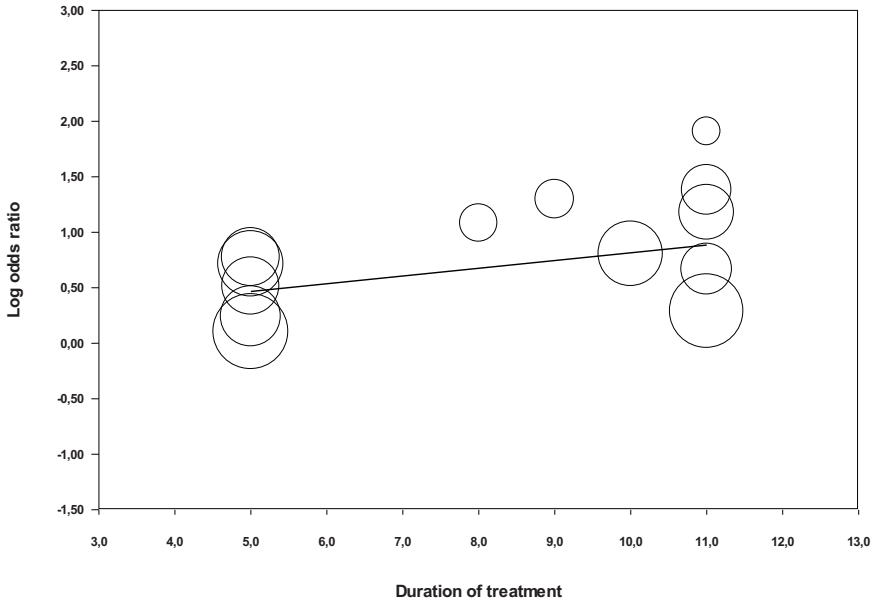


Figure c. Meta-regression of analysis of the association between treatment duration and treatment response (Full sample)

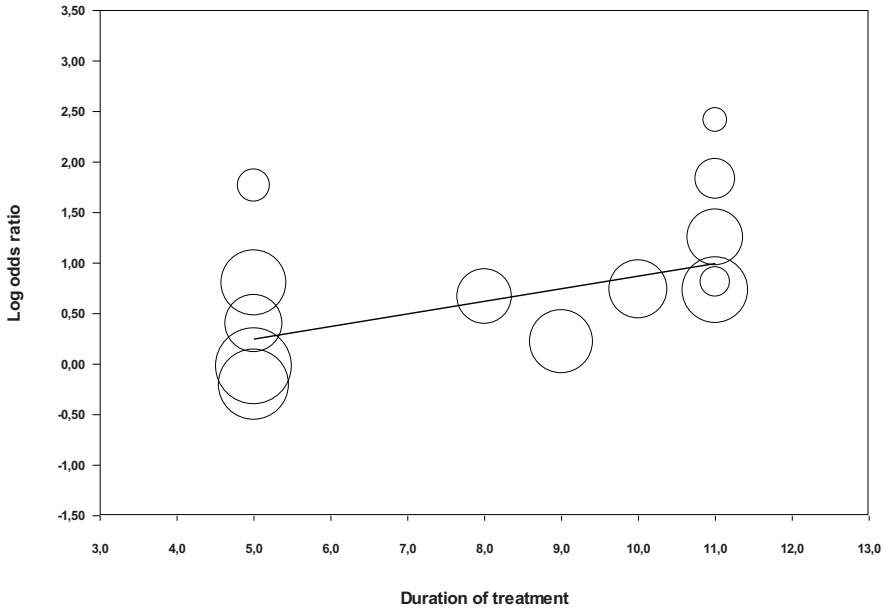


Figure d. Meta-regression of analysis of the association between treatment duration and treatment response (complete cases sample)

E3. SUPPLEMENTAL MATERIAL

Generic IPD Protocol

The methods of the IPD meta-analysis should be in compliance with the PRISMA IPD statement (Stewart et al., 2015)

- Identification and selection of studies:
- An existing database on psychological treatments for adult depression will be used. This database has been developed in 2006 and it is updated annually by a systematic literature search in the databases of PubMed, PsycINFO, Embase and the Cochrane Library (Cuijpers, van Straten, Andersson, & van Oppen, 2008). Two researchers will examine the papers for eligibility. In case of disagreement, consensus will be sought, and if needed a third senior researcher will be consulted.
- Primary studies from meta-analyses of psychological treatment for depression will be also checked to ensure that no published studies are missing.
- In addition, the research team will ask key researchers in the field if they are aware of unpublished trials on the topic of interest.

The inclusion process of the studies will be reported in a PRISMA IPD flow chart.

Data acquisition:

Frist or senior authors of eligible papers will be contacted requesting permission to use their datasets. If there is no response, reminders will be sent two weeks and one month after the first contact. If there is no response after one month, the trial will be excluded as 'unavailable'

Data extraction:

- Data to be extracted from RCTs are:
- Reference
- The year of publication
- Country
- Recruitment (e.g. community, primary care)
- Patient characteristics (e.g. target group, the anonymised unique patient identifier)
- Therapy characteristics (e.g. type of psychotherapy, treatment format, duration, etc.)
- Group variable (randomized group)
- Control characteristics (e.g. type of control)
- Comorbidities (e.g. comorbid anxiety disorder)
- Outcome data (continuous depression scores at baseline, post-treatment and follow up assessments)
- Demographic characteristics (e.g. age, gender, educational status, marital status, employment status)
- Data related to risk of bias assessment

Included studies will be described in text and tables. Two researchers will extract data independently; potential disagreements will be solved through discussion and if need the project coordinator will be consulted.

Checking Data:

After receiving databases from authors the following should be checked with the publish paper:

- The means and standard deviations of the continuous depression measure, age, and any other continuous measure.
- The frequencies of gender, and a few other reported demographic or clinical characteristics.
- Where possible, the post-treatment means with the papers and rates of missing data/ dropout.

Entering Data:

- All patients that are randomized from each RCT should be included into the merged IPD database.
- Variables from primary RCTs will be recoded according to the merged IPD database coding.

Risk of bias assessment:

The validity of included studies will be assessed using the criteria of the Cochrane Collaboration Risk of bias assessment tool (Higgins & Altman, 2008). Two reviewers will conduct assessment of the quality independently. In case of unclear items, the primary authors of the included RCTs will be asked to provide clarifications.

Data Analysis

- Mixed models will be used for the regression analysis (building a model with an interaction effect between the variable of interest and treatment group).
- In case of varying outcome measures (dependent variables), the measures will be standardized. Dichotomous variables (e.g. response) can also be used. It is preferable to do both of these procedures, and use one as a sensitivity analysis.
- The current state of the field suggests using multiple imputations to deal with missing data. Complete cases analysis will follow to ensure robustness of the results.
- In case of missing studies, a traditional meta-analysis will be performed to examine differences between studies that provided data and studies that did not.

Traditional Meta-analysis (continued)

We used data reported in the published papers to calculate the effect sizes (Hedges' g) showing the difference between self-guided iCBT and control conditions on depressive symptoms severity. Hedges' g is the difference between the average score of the self-guided iCBT group and the average score of the control group at the post-treatment assessment, divided by the pooled standard deviation, adjusting for small sample bias. Hedges's g of 0.2 is considered to be small, 0.5 as moderate and 0.8 as large(Cohen, 1988). The difference between studies that did and did not provide data was tested in a subgroup analysis. Heterogeneity was examined by calculating I^2 indicating heterogeneity as a percentage (with 25% as low, 50% as moderate, and 75% as high)(Higgins & Thompson, 2002). The 95% confidence intervals (CI) around I^2 were calculated using the non-central chi-squared-based approach in the heterogi module of Stata(Evangelou, Ioannidis, & Patsopoulos, 2007; Orsini, Bottai, Higgins, & Buchan, 2006). We examined publication bias by visually inspecting the funnel plot, by using the trim and fill procedure and Egger's test of funnel plot asymmetry(Duval & Tweedie, 2000; Egger, Smith, Schneider, & Minder, 1997).

APPENDIX F (CHAPTER 9)

F1. TABLES

Table a. Relative odds of deterioration of self-guided iCBT versus controls in adults with depressive symptoms, two-stage IPD

Outcomes	'Reliable deterioration'						'Any deterioration'					
	N	OR	95% CI[b]	I^2	95%CI	p[c]	N	OR	95% CI[b]	I^2	95%CI	p[c]
Full sample	13	0.62	0.48 to 0.81	0%	0 to 57%	.000	13	0.63	0.51 to 0.77	41%	0 to 69%	.000
Subgroups												
Type of control												
TAU vs.	4	0.76	0.51 to 1.13	15%	0 to 85%	.16	4	0.68	0.45 to 1.03	63%	0 to 88%	.62
Other	9	0.51	0.35 to 0.75	0%	0 to 65%		9	0.60	0.47 to 0.76	31%	0 to 68%	
Recruitment												
Community	7	0.47	0.30 to 0.74	0%	0 to 71%	.29	7	0.56	0.41 to 0.75	36%	0 to 73%	0.39
Community and/or primary care	4	0.76	0.51 to 1.13	15%	0 to 85%		4	0.68	0.45 to 1.03	63%	0 to 88%	
Other	2	0.64	0.32 to 1.30	0%	N/A		2	0.75	0.54 to 1.03	0%	N/A	
Support												
Pure self-guided iCBT	9	0.61	0.45 to 0.83	0%	0 to 65%	.82	9	0.59	0.46 to 0.77	48%	0 to 76%	.34
Technically supported iCBT	4	0.66	0.39 to 1.13	0%	0 to 85%		4	0.72	0.53 to 0.96	16%	0 to 87%	
Complete case	13	0.61	0.45 to 0.83	0%	0 to 57%	.000	13	0.61	0.48 to 0.79	50%	5 to 74%	.000
Subgroups												
Type of control												
TAU vs.	4	0.85	0.50 to 1.44	36%	0 to 78%	.06	4	0.69	0.40 to 1.19	74%	26 to 91%	.56
Other	9	0.43	0.27 to 0.70	0%	0 to 65%		9	0.59	0.44 to 0.76	31%	0 to 68%	
Recruitment												
Community	7	0.40	0.23 to 0.70	0%	0 to 71%	.16	7	0.54	0.37 to 0.79	47%	0 to 77%	.69
Community and/or primary care	4	0.85	0.50 to 1.44	36%	0 to 78%		4	0.69	0.40 to 1.19	74%	26 to 91%	
Other	2	0.56	0.19 to 1.59	0%	N/A		2	0.67	0.44 to 1.01	0%	N/A	
Support												
Pure self-guided iCBT	9	0.60	0.43 to 0.85	0%	0 to 65%	.85	9	0.57	0.41 to 0.78	53%	0 to 78%	.34
Technically supported iCBT	4	0.65	0.34 to 1.23	3%	0 to 85%		4	0.73	0.49 to 0.80	40%	0 to 80%	

I^2: heterogeneity index; N: Number of studies; N/A: Not applicable; OR: Odds Ratio
[b] 95% CI: 95% Confidence Intervals; p: p-value
[c] p-value between groups

APPENDIX G (CHAPTER 10)

G1. TABLES

Table a. Selected characteristics of randomised controlled studies examining the effects of internet-based psychotherapies for depression in adults.

Study	Recr	Depression	Inter-vention	N_{mod}	Time (wks)	Guidance	N	Control group	N	Primary outcome	Duration of follow-up	Qual [a)]	Country
Andersson et al. (2005)	Comm	MDD (CIDI)	CBT	5	8	Feedback on answers given in end of modules	62	Web-based discussion group	62	BDI-II	6 months	+ + + +	SE
Berger et al. (2011)	Comm	MDD (MINI)	CBT	11	12	Scheduled weekly therapist support via email	25	WL	26	BDI-II	6 months	+ + + +	CH/DE
Buntrock et al. (2015)	Comm	CES-D ≥ 16	CBT	6	6	Feedback after each module by an online trainer	201	Web-based Psychoeducation	204	CES-D	6 months	+ + + +	DE
Carlbring et al. (2013)(	Comm	MDD (MINI)	ACT	7	13	Weekly contact by psychologist	40	WL	40	BDI-II	N/A	+ + + +	SE
Choi et al. (2012)	Comm	MDD (SCID-I)	CBT	6	8	Weekly telephone/email support	25	WL	30	BDI	N/A	+ + – +	AU
Ebert et al. (2014)	Comm	CES-D ≥ 16	PST	5	5	Feedback on answers given by a coach at the end of each module	75	WL	75	CES-D	3 & 6 months	+ + + +	DE
Geraedts et al. (2014)	Comm	CES-D ≥16	PST	6	6	Feedback on weekly assignments given by a coach	116	TAU	115	CES-D	6 & 12 months	+ + + +	NL
Hallgren et al. (2015)	Clinical	PHQ-9 > 9	CBT	14	12	Progress was monitored by a clinician who provided support if needed	317	TAU	312	MADRS	3 months	+ + + +	SE

continued

Table a. Selected characteristics of randomised controlled studies examining the effects of internet-based psychotherapies for depression in adults. (continued)

Study	Recr	Depression	Inter-vention	N_{mod}	Time (wks)	Guidance	N	Control group	N	Primary outcome	Duration of follow-up	Qual [a)]	Country
Imamura et al. (2014)	Clinical	Depressive symptoms; not MDD (CIDI)	CBT	6	10	Participants progress (modules completed and homework) were monitored through emails	381	Info regarding stress management	381	BDI-II	3 & 6 months	+ + + +	JP
Johansson et al. (2012)	Comm/Clin	MDD (DSM-IV)	PD	9	10	Online therapist contact	46	Brief scheduled therapist support	46	BDI-II	10 months	+ + - +	SE
Johansson et al. (2012)b	Comm/Clin	MADRS-S >14 MDD on SCID-I	CBT*	8-10	10	Therapist contact via email	37 36	Moderated web-based discussion group	42	BDI-II	N/A	+ + + +	SE
Kenter et al. (2016)	Clinical	MDD (CIDI)	PST	5	5	Brief weekly emails by a coach	136	Self-help book	133	CES-D	6 & 12 months	+ + + +	NL
Kivi et al. (2014)	Clinical	MDD (MINI)	CBT	7	12	Email/telephone call by therapists	44	TAU	46	BDI-II	N/A	+ + + +	SE
Klein et al. (2016)	Comm/Clin	PHQ-9 > 9	CBT	11	12	Feedback on weekly base by a coach through email	316	TAU	316	PHQ-9	6 months	+ + + +	DE
Newby et al. (2013)	Comm/Clin	MDD (MINI)	CBT	6	10	Regular contact up to session 2, and the response to user requests or decline in K10/PHQ9 scores	25	WL	37	BDI-II	N/A	+ + – +	AU
Nobis et al. (2015)	Clinical	MDD (SCID-I)	PST	5	5	Coaches provided personalized feedback by emails	130	Web-based Psychoeducation	130	CES-D	6&18 months	+ + + +	DE
Perini et al. (2009)	Comm	PHQ-9 score > 4	CBT	6	6	Email contact by therapist	27	WL	18	BDI-II	N/A	+ + + +	AU
Ruwaard et al. (2009)	Comm	BDI-IA 10-29	CBT	8	11	Therapist feedback on activities	36	WL	18	BDI-IA	N/A	+ + + +	NL

continued

Table a. Selected characteristics of randomised controlled studies examining the effects of internet-based psychotherapies for depression in adults. (continued)

Study	Recr	Depression	Inter-vention	N_{mod}	Time (wks)	Guidance	N	Control group	N	Primary outcome	Duration of follow-up	Qual [a)]	Country
Sheeber et al. (2012)	Clin	CES-D ≥ 21	CBT	8	8	Weekly scheduled telephone calls	35	WL	35	BDI-II	N/A	+ + + +	US
Unlu et al. (2012)	Comm	MDD (MINI)	PST	5	5	Feedback on homework activities by coach	49	WL	47	CES-D	4 months	+ + + +	NL
Van Bastelaar et al. (2011)	Comm	MDD (CIDI)	CBT	8	8	Feedback on homework activities by coach	125	WL	130	CES-D	1 month	+ + – +	NL
Vernmark et al. (2010)	Comm	MDD (SCID-I)	CBT	7	7	Email support from therapist	29	WL	29	BDI	N/A	+ + - +	SE
Warmerdam et al. (2008)	Comm	CES-D ≥ 16	CBT	8	8	Weekly feedback from therapist	88	WL	87	CES-D	3 months	+ + + +	NL
			PST	5	8		88						
Williams et al. (2013)	Comm/Clin	MDD (MINI)	CBM & CBT	6	10	Standard email contact and phone contact in response to user requests or decline in K10/PHQ9 scores.	38	WL	31	BDI-II	N/A	+ + + +	AU

Abbreviations: ACT: Acceptance and Commitment therapy; AU: Australia; BDI, Beck Depression Inventory; CBM: Cognitive Bias Modification; CBT: Cognitive behaviour therapy; CES-D: Centre for Epidemiology Studies Depression Scale;
CIDI: Composite Interventional Diagnostic Interview; Clin: Clinical Sample; Comm: Community sample; DE: Germany; Depression: confirmation of depression; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders – 4th edition;
JP: Japan; MADRS: Montgomery–Asberg Depression Rating Scale; NL: Netherlands; Nmod: Number of modules in the intervention; PD: Psychodynamic therapy; PHQ-9: Patient Health Questionnaire-9 items; PST: Problem-solving therapy; Qual: Risk of Bias Score; Recr, Recruitment population; SE: Sweden; SW: Switzerland; TAU: Treatment As Usual; US: the United States; WL: waiting list control;

[a] In this column a positive or negative sign is given for four quality criteria, respectively: allocation sequence; concealment of allocation to conditions; blinding of assessors; and intention-to-treat analyses.

[b] Klein et al. (2016) trial provided unguided treatment to participants with mild depressive symptoms at the baseline, while participants with moderate symptoms of depression (PHQ-9 > 9) received therapeutic support. Participants of this trial were stratified by severity of depression during randomization and thus, we decided to exclude all participants who did not receive therapeutic support (PHQ-9 < 10; n = 379) from all the analyses of the present IPD meta-analysis.

Table b. Demographic and clinical characteristics

	Intervention (N = 2514)			Control (N = 2375)			All (N = 4889)		
	%	M	SD	%	M	SD	%	M	SD
Age		42.5	11.9		42.3	11.9		42.4	11.9
Female	60.04			58.14			59.11		
Married/Partnership	49.35			47.34			48.32		
Further education after high school [a]	65.18			65.65			66.45		
European ethnicity	43.78			43.57			43.67		
Employed	78.52			78.67			78.60		
BDI									
Baseline		19.43	10.18		18.86	10.34		19.16	10.25
Post		12.51	9.08		16.59	10.24		14.62	9.91
FU		11.74	9.54		12.62	9.09		12.16	9.34
CES-D									
Baseline		29.53	9.27		29.11	9.28		29.33	9.27
Post		19.44	10.9		23.94	10.56		21.76	10.96
FU		17.92	10.86		20.98	10.84		19.50	10.95
PHQ-9									
Baseline		11.81	1.39		11.89	1.31		11.85	1.35
Post		8.02	4.12		9.94	4.56		8.99	4.45
FU		7.86	4.25		9.42	4.44		8.65	4.41

continued

Table b. Demographic and clinical characteristics (continued)

	Intervention (N = 2514)			Control (N = 2375)			All (N = 4889)		
	%	M	SD	%	M	SD	%	M	SD
MADRS									
Baseline		21.91	7.10		20.82	7.19		21.36	7.16
Post		11.20	7.36		13.69	8.99		12.39	8.31
FU		9.83	7.88		11.22	8.85		10.50	8.38
No current use of antidepressants	73.58			72.10			72.85		
Comorbid anxiety	57.15			55.39			56.29		
Number of previous episodes odepression		1.93	3.65		1.87	4.87		1.91	4.29
Problematic alcohol drinking	18.10			19.07			18.59		

Abbreviations: BDI: Beck Depression Inventory; CES-D: Centre for Epidemiological Studies Depression Scale; FU: Follow-up; M: Mean; MADRS: Montgomery–Asberg Depression Rating Scale; N: Number; PHQ-9: Patient Health Questionnaire - 9 items; SD: Standard Deviation
Note: Percentages refer to those participants of studies who reported data.

Table c. Relative odds of deterioration of remission and response versus controls in adults with depressive symptoms, two-stage IPD

	Response						Remission					
Outcomes	**N**	**OR**	**95% CI[b]**	**I^2**	**95%CI**	**p[c]**	**N**	**OR**	**95% CI[b]**	**I^2**	**95%CI**	**p[c]**
Full sample												
Main effects	26	2.76	2.23 – 3.41	58%	35 – 73%	<.001	26	2.80	2.21 – 3.56	54%	29 – 71%	<.001
Subgroups												
Diagnosis												
Depressive symptoms vs.	13	2.49	1.93 – 3.23	61%	28 – 79%	.25	13	2.54	1.92 – 3.37	56%	19 – 77%	.34
Major Depression	13	3.26	2.23 – 4.76	57%	19 – 77%		13	3.29	2.12 – 5.11	52%	11 – 75%	
Target group												
General vs.	21	2.99	2.36 – 3.79	49%	15 – 69%	.20	21	3.02	2.24 – 4.08	54%	25 – 72	.46
Specific population	5	2.08	1.26 – 3.46	78%	48 – 91%		5	2.47	1.58 – 3.87	64%	7 – 86%	
Type of control												
Active vs.	12	2.30	1.78 – 2.98	62%	29 – 80%	.05	12	2.36	1.82 – 3.06	55%	13 – 76%	.08
Non active controls	14	3.49	2.49 – 4.89	45%	0 – 70%		14	3.73	2.38 – 5.83	46%	0 – 71%	
Recruitment												
Community and/or primary care vs.	12	2.70	1.91 – 3.81	70%	46 – 84%	.81	12	2.91	1.98 – 4.29	68%	42 – 83%	.85
Community only	14	2.84	2.19 – 3.67	37%	0 – 67%		14	2.78	2.06 – 3.74	31%	0 – 64%	
Outcome measure												
BDI vs.	16	3.28	2.32 – 4.63	52%	15 – 73%	.17	16	3.64	2.33 – 5.69	58%	27 – 76%	.11
Other	10	2.41	1.83 – 3.15	66%	33 – 83%		10	2.38	1.84 – 3.09	50%	0 – 76%	
Number of online sessions												
4-5 vs.	8	2.67	1.64 – 4.36	72%	41 – 86%		8	2.45	1.55 – 3.88	49%	0 – 77%	
6-7 vs.	9	2.90	1.90 – 4.43	67%	34 – 84%	.86	9	2.96	1.87 – 4.71	61%	19 – 81%	.72
≥ 8	9	2.54	1.99 – 3.25	21%	0 – 63%		9	3.16	2.07 – 4.83	60%	17 – 81%	
Intervention type												
CBT vs.	20	2.67	2.13 – 3.36	52%	20 – 71%	.74	20	2.70	2.07 – 3.54	53%	22 – 72%	.64
Other	6	2.96	1.67 – 5.25	74%	41 – 89%		6	3.15	1.78 – 5.56	60%	1 – 84%	

continued

Table c. Relative odds of deterioration of remission and response versus controls in adults with depressive symptoms, two-stage IPD (continued)

	Response						Remission					
Outcomes	**N**	**OR**	**95% CI[b]**	**I^2**	**95%CI**	**p[c]**	**N**	**OR**	**95% CI[b]**	**I^2**	**95%CI**	**p[c]**
Risk of bias												
Low (4)	22	2.67	2.12 – 3.34	62%	39 – 76%	.28	22	2.62	2.06 – 3.31	50%	19 – 70%	.38
Some risk (< 4)	4	3.69	2.13 – 6.40	0%	0 – 85%		4	4.23	1.49 – 12.05	66%	0 – 88%	
Complete cases												
Main effects	26	2.84	2.19 – 3.68	63%	44-76%	<.001	26	2.91	2.19 – 3.86	59%	37 – 73%	<.001
Subgroups												
Diagnosis												
Depressive symptoms vs.	13	2.58	1.88 – 3.53	66%	39 – 81%	.37	13	2.68	1.87 – 3.85	65%	36 – 80%	.52
Major Depression	13	3.32	2.08 – 5.29	63%	33 – 80%		13	3.26	2.04 – 5.20	50%	7 – 74%	
Target group												
General vs.	21	3.08	2.32 – 4.10	57%	30 – 73%	.28	21	3.06	2.21 – 4.24	53%	23 – 72%	.53
Specific population	5	2.08	1.09 – 3.98	80%	53 – 92%		5	2.41	1.20 – 4.81	77%	46 – 91%	
Type of control												
Active vs.	12	2.19	1.57 – 3.07	71%	48 – 84%	.02	12	2.36	1.71 – 3.25	62%	29 – 80%	.08
Non active controls	14	3.84	2.76 – 5.33	26%	0 – 61%		14	3.79	2.44 – 6.39	42%	0 – 69%	
Recruitment												
Community and/or primary care vs.	12	2.62	1.74 – 3.94	73%	51 – 85%	.57	12	3.01	1.93 – 4.69	70%	36– 84%	.90
Community only	14	3.08	2.22 – 4.28	49%	7 – 72%		14	2.90	1.99 – 4.23	43%	0 – 70%	
Outcome measure												
BDI vs.	16	3.42	2.28 – 5.11	55%	22 – 75%	.20	16	3.61	2.17 – 6.01	62%	34 – 78%	.22
Other	10	2.42	1.70 – 3.43	73%	49 – 86%		8	2.47	1.79 – 3.42	57%	19 – 79%	
Number of online sessions												
4-5 vs.	8	2.75	1.49 – 5.09	76%	51 – 88%		8	2.53	1.35 – 4.72	61%	15 – 82%	
6-7 vs.	9	2.83	1.71 – 4.68	71%	43 – 85%	.99	9	2.93	1.72 – 4.96	64%	27 – 83%	.81
≥ 8	9	2.76	2.02 – 3.78	35%	0 – 70%		9	2.27	2.06 – 5.19	60%	17 – 81%	

continued

Table c. Relative odds of deterioration of remission and response versus controls in adults with depressive symptoms, two-stage IPD (continued)

	Response						Remission					
Outcomes	**N**	**OR**	**95% CI[b]**	**I^2**	**95%CI**	**p[c]**	**N**	**OR**	**95% CI[b]**	**I^2**	**95%CI**	**p[c]**
Intervention type												
CBT vs.	20	2.76	2.11 – 3.63	55%	26 – 73%	.87	20	2.77	2.02 – 3.70	57%	28 – 74%	.63
Other	6	2.92	1.42 – 6.04	88%	58 – 91%		6	3.33	1.68 – 6.59	66%	18 – 86%	
Risk of bias												
Low (4)	22	2.71	2.06 – 3.58	66%	48 – 79%	.26	22	2.69	2.02 – 3.57	56%	28 – 72%	.35
Some risk (< 4)	4	3.96	2.19 – 7.15	1%	0 – 85%		4	4.54	1.55 – 13.26	65%	0 – 88%	

I^2: heterogeneity index; BDI: Beck Depression Inventory; N: Number of studies; OR: Odds Ratio

[b] 95% CI: 95% Confidence Intervals; p: p-value

[c] p-value between groups

G2. FIGURES

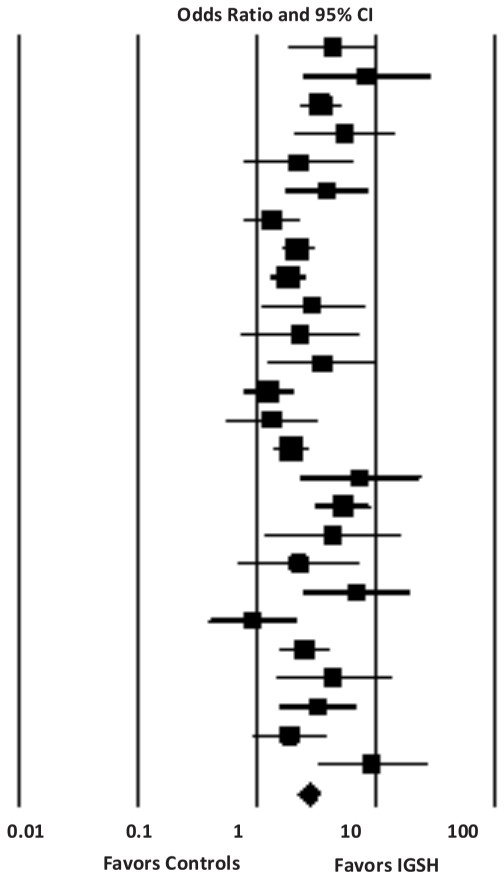
Figure a. Forest plot of remission – 2 stage IPD

Study name	Odds ratio	Low limit	Upper limit	p-Value
Andersson, 2005	3.73	1.13	12.37	0.03
Berger, 2011	9.43	1.82	48.83	0.01
Buntrock, 2015	3.79	2.07	6.93	0.00
Carlbring, 2013	4.85	1.43	16.42	0.01
Choi, 2012	1.00	0.27	3.77	1.00
Ebert, 2014	4.58	0.50	42.23	0.18
Geraedts, 2014	2.42	1.36	4.28	0.00
Hallgren, 2015	1.61	1.15	2.26	0.01
Imamura, 2014	1.92	1.38	2.66	0.00
Johansson, 2012	5.12	2.05	12.76	0.00
Johansson, 2012b (standardized)	2.41	0.59	9.81	0.22
Johansson, 2012b (tailored)	6.88	1.41	33.54	0.02
Kenter, 2016	1.39	0.78	2.47	0.27
Kivi, 2014	1.22	0.51	2.96	0.65
Klein, 2016	1.98	1.44	2.72	0.00
Newby, 2013	22.27	4.37	113.58	0.00
Nobis, 2013	5.29	2.73	10.24	0.00
Perini, 2009	8.62	1.65	44.97	0.01
Ruwaard, 2009	6.25	1.54	25.42	0.01
Sheeber, 2012	23.80	2.91	194.86	0.00
Unlu, 2013	0.80	0.25	2.58	0.70
van Bastelaar, 2011	3.06	1.66	5.64	0.00
Vernmark, 2010	3.58	1.13	11.37	0.03
Warmerdam, 2008 (CBT)	2.63	1.15	5.98	0.02
Warmerdam, 2008 (PST)	2.09	0.98	4.48	0.06
Williams, 2013	7.20	1.45	35.72	0.02
Overall	2.80	2.21	3.56	0.00

A

Figure b. Forest plot of response – 2 stage IPD

Study name	Odds ratio	Low limit	Upper limit	p-Value
Andersson, 2005	4.43	1.83	10.68	0.00
Berger, 2011	8.57	2.42	30.30	0.00
Buntrock, 2015	3.45	2.28	5.22	0.00
Carlbring, 2013	5.48	2.10	14.28	0.00
Choi, 2012	2.25	0.76	6.65	0.14
Ebert, 2014	3.91	1.74	8.79	0.00
Geraedts, 2014	1.34	0.80	2.26	0.26
Hallgren, 2015	2.24	1.62	3.08	0.00
Imamura, 2014	1.88	1.31	2.71	0.00
Johansson, 2012	2.97	1.08	8.14	0.03
Johansson, 2012b (standardized)	2.33	0.74	7.33	0.15
Johansson, 2012b (tailored)	3.57	1.22	10.43	0.02
Kenter, 2016	1.27	0.79	2.06	0.32
Kivi, 2014	1.35	0.56	3.25	0.50
Klein, 2016	1.96	1.41	2.73	0.00
Newby, 2013	7.38	2.25	24.27	0.00
Nobis, 2013	5.35	3.10	9.22	0.00
Perini, 2009	4.37	1.19	16.04	0.03
Ruwaard, 2009	2.27	0.71	7.28	0.17
Sheeber, 2012	6.94	2.41	19.99	0.00
Unlu, 2013	0.94	0.40	2.23	0.89
van Bastelaar, 2011	2.56	1.55	4.25	0.00
Vernmark, 2010	4.45	1.44	13.74	0.01
Warmerdam, 2008 (CBT)	3.29	1.53	7.10	0.00
Warmerdam, 2008 (PST)	1.90	0.91	3.97	0.09
Williams, 2013	9.38	3.21	27.35	0.00
Overall	2.76	2.23	3.41	0.00



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About the author

Eirini Karyotaki was born in Iraklion of Crete, Greece. In 2010, she has been graduated from the National and Kapodistrian University of Athens and in 2011 she followed a 2-years research masters on Clinical and Developmental Psychopathology at the VU in Amsterdam, the Netherlands. Since 2013 she is working as a PhD Candidate at the department of Clinical Psychology in VU, Amsterdam.

Her research focuses on examining the effectiveness of psychotherapy in treating adult depression, with a special interest in internet-based interventions. During her Ph.D. trajectory, she focused on systematic reviews with specialization on conventional and individual participant data meta-analyses. She has been involved in several international projects, such as the E-Compared project (2014 – present), which examines the clinical and cost-effectiveness of blended depression treatment. Moreover, she has built the evidence profiles on depression for the development of several treatment guidelines; including the Clinical practice guideline on major depression of the Belgian health care institute KCE (2013 – 2014), the update of the World Health Organization (WHO) mental health gap program (2015) and the guidelines of the American Psychological Association (APA) on Elderly Depression (2015). Currently she is coordinating a large-scale university project on college students' mental health, namely the Caring Universities, which involves epidemiological, effectiveness and implementation research (2016 – present). The Caring Universities project is an international endeavour in collaboration with the WHO World Mental Health Survey Initiative, which is led by Harvard Medical School.

Along with research, Eirini Karyotaki is a lecturer in the courses of Psychopathology (2014 – present) and Systematic Reviews and Meta-analyses (2013 – present) in the first year of the research masters in Clinical and Developmental Psychopathology at the VU, Amsterdam. She is also a guest lecturer in the course on Systematic Reviews in RINO, Amsterdam (2015 – present). She has supervised nine master theses, three of which got published in peer reviewed journals (2013 – 2017).

Eirini Karyotaki has given presentations of her work in eight international conferences, such as the conference of the International and European Society for Research on Internet Interventions (ISSRI and ESSRI) and the World Congress of Psychiatry (WPA XVII) (2013 – 2017). A full list of her publications is given in the next section of this thesis.

A

Publications of Eirini Karyotaki

1. Bolinski, F., Kleiboer, A., Bosmans, J.E., Cuijpers, P., Karyotaki, E., Jacobi, C., Ebert, D.D., Riper, H. (Submitted). Effectiveness of a Transdiagnostic Internet- and Mobile-Supported Intervention for the Prevention of Depression and Anxiety (ICare Prevent) in Dutch College Students: Study protocol for a Randomized Controlled Trial. Trials.
2. Boumparis, N., Karyotaki, E., Kleiboer, A., Hofmann, S. G., & Cuijpers, P. (2016). The effect of psychotherapeutic interventions on positive and negative affect in depression: A systematic review and meta-analysis. *Journal of Affective Disorders*, 202, 153-162.
3. Boumparis, N., Karyotaki, E., Schaub, M. P., Cuijpers, P., & Riper, H. (2017). Internet Interventions for Adult Illicit Substance Users: A Meta-analysis. *Addiction*. 112(9):1521-1532.
4. Cristea, I.A., Stefan, S., Karyotaki, E., David, D., Hollon, S., & Cuijpers, P. (In press). The Effects of Cognitive Behavioral Therapy Are Not Systematically Falling: A Revision of Johnsen & Friborg (2015). *Psychological Bulletin*. 143(3):326-340
5. Cuijpers, P., Cristea, I. A., Karyotaki, E., Reijnders, M., & Huibers, M. J. (2016). How effective are cognitive behavior therapies for major depression and anxiety disorders? A meta-analytic update of the evidence. *World Psychiatry*, 15(3), 245-258.
6. Cuijpers, P., Cristea, I., Karyotaki, E., Reijnders, M., Hollon, S. (Submitted). Component studies of psychological treatments of adult depression: A systematic review and meta-analysis. *Psychological Medicine*.
7. Cuijpers, P., Cristea, I.A., Karyotaki, E., Reijnders, M., & Huibers, M. (2016). How effective are cognitive behavior therapies for major depression and anxiety disorders? A meta-analytic update of the evidence. *World Psychiatry*, 15, 245-258.
8. Cuijpers, P., Karyotaki, E., Andersson, G., Li, J., Mergl, R., & Hegerl, U. (2015). The effects of blinding on the outcomes of psychotherapy and pharmacotherapy for adult depression: A meta-analysis. *European Psychiatry*, 30(6), 685-693.
9. Cuijpers, P., Karyotaki, E., Pot, A. M., Park, M., & Reynolds, C. F., 3rd. (2014). Managing depression in older age: psychological interventions. *Maturitas*, 79(2), 160-169.
10. Cuijpers, P., Karyotaki, E., Reijnders, M., & Huibers, M. J. (Submitted). Who benefits from psychotherapies for adult depression? A meta-analytic study. *Lancet Psychiatry*.
11. Cuijpers, P., Karyotaki, E., Reijnders, M., Ebert, D.D. (Submitted). Was Eysenck right after all? A reassessment of the effects of psychotherapy for adult depression. *Perspectives on Psychological Science*.
12. Cuijpers, P., Karyotaki, E., Reijnders, M., Purgato, M., & Barbui, C. (In press). Psychotherapies for depression in low- and middle-income countries: a meta-analysis. *World Psychiatry*.
13. Cuijpers, P., Karyotaki, E., Weitz, E., Andersson, G., Hollon, S. D., & van Straten, A. (2014). The effects of psychotherapies for major depression in adults on remission, recovery and improvement: a meta-analysis. *Journal of Affective Disorders*, 159, 118-126.
14. Cuijpers, P., Kleiboer, A., Karyotaki, E., & Riper, H. (2017). Internet and mobile interventions for depression: Opportunities and challenges. *Anxiety and Depression*. 34(7):596-602
15. Cuijpers, P., Weitz, E., Karyotaki, E., Garber, J., & Andersson, G. (2015). The effects of psychological treatment of maternal depression on children and parental functioning: a meta-analysis. *European Child Adolescent Psychiatry*, 24(2), 237-245.

16. Karyotaki, E., Ebert, D.D., Donkin, L., Riper, H., Twisk, J., Burger, S., ... , Cuijpers, P. (Submitted). Does Internet-Based Guided Self-Help Result in Clinically Relevant Changes for Patients with Depression? An Individual Participant Data Meta-Analysis. *Lancet Psychiatry*.

17. Karyotaki, E., Kemmeren, L., Riper, H., Twisk, J., Hoogendoorn, A., Kleiboer, A., . . . Cuijpers, P. (Submitted). Is self-guided Internet-based Cognitive Behavioural Therapy (iCBT) harmful? An individual participant data meta-analysis. *Psychological Medicine*.

18. Karyotaki, E., Kleiboer, A., Smit, F., Turner, D. T., Pastor, A. M., Andersson, G., . . . Cuijpers, P. (2015). Predictors of treatment dropout in self-guided web-based interventions for depression: an 'individual patient data' meta-analysis. *Psychological Medicine*, 45(13), 2717-2726.

19. Karyotaki, E., Riper, H., & Cuijpers, P. (2017). Internet-Based Self-Help Interventions for Depression in Routine Care—Reply. *Jama Psychiatry*, 74(8), 853-853.

20. Karyotaki, E., Riper, H., Twisk, J., Hoogendoorn, A., Kleiboer, A., Mira, A., . . . Cuijpers, P. (2017). Efficacy of Self-guided Internet-Based Cognitive Behavioral Therapy in the Treatment of Depressive Symptoms: A Meta-analysis of Individual Participant Data. *JAMA Psychiatry*. 74(4), 351-359.

21. Karyotaki, E., Smit, Y., de Beurs, D. P., Henningsen, K. H., Robays, J., Huibers, M. J., … Cuijpers, P. (2016). The long-term efficacy of acute phase psychotherapy for depression: a meta-analysis of randomised trials. *Depression and Anxiety*, 33(5), 370-383.

22. Karyotaki, E., Smit, Y., Holdt Henningsen, K., Huibers, M. J., Robays, J., de Beurs, D., & Cuijpers, P. (2016). Combining pharmacotherapy and psychotherapy or monotherapy for major depression? A meta-analysis on the long-term effects. *Journal of Affective Disorders*, 194, 144-152.

23. Karyotaki, E., Tordrup, D., Buntrock, C., Bertollini, R., & Cuijpers, P. (2016). Economic evidence for the clinical management of major depressive disorder: a systematic review and quality appraisal of economic evaluations alongside randomised controlled trials. *Epidemiology and Psychiatry Science*, 1-16.

24. Turner, D. T., van der Gaag, M., Karyotaki, E., & Cuijpers, P. (2014). Psychological interventions for psychosis: a meta-analysis of comparative outcome studies. *American Journal of Psychiatry*, 171(5), 523-538.

25. Turner, D., McGlanaghy, E., Hutton, P., Cuijpers, P., van der Gaag, M., Karyotaki, E., MacBeth, A. (Submitted). A meta-analysis of social skills training and related interventions for psychosis. *Schizophrenia Bulletin*.

26. van Ballegooijen, W., Cuijpers, P., van Straten, A., Karyotaki, E., Andersson, G., Smit, J. H., & Riper, H. (2014). Adherence to Internet-based and face-to-face cognitive behavioural therapy for depression: a meta-analysis. *PLoS One*, 9(7), e100674.

27. van Ballegooijen, W., Ruwaard, J., Karyotaki, E., Ebert, D. D., Smit, J. H., & Riper, H. (2016). Reactivity to smartphone-based ecological momentary assessment of depressive symptoms (MoodMonitor): protocol of a randomised controlled trial. *BMC Psychiatry*, 16(1), 359.

28. Wierda, M., Smit, Y., Begeer, S., Parmentier, C.C., Bruel, A. van den, Karyotaki, E., Koot, J.M. & Cuijpers, P. (2014). De effectiviteit van EIBI en DTT bij kinderen met een autismespectrumstoornis en/of een verstandelijke beperking. (Advisory Report). Amsterdam: *Vrije Universiteit Amsterdam*.

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